# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 215904Orig1s000

# STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **NDA/BLA #:** | NDA 215904 |
| **Drug Name:** | Ganaxolone (Ztalmy) |
| **Indication(s):** | Seizures associated with Cyclin-dependent Kinase-like 5 Deficiency Disorder (CDD) |
| **Applicant:** | Marinus Pharmaceuticals, Inc |
| **Date(s):** | Submission date: 7/20/2021 |
| | PDUFA Date: 3/20/2022 |
| **Review Priority:** | Priority |
| | |
| **Biometrics Division:** | Division of Biometrics I |
| **Statistical Reviewer:** | Xiang Ling, Ph.D. |
| **Concurring Reviewers:** | John Lawrence, Ph.D., Team Leader |
| | James Hung, Ph.D., Director |
| **Medical Division:** | Division of Neurology 2 |
| **Clinical Team:** | Steven Dinsmore, M.D., Clinical reviewer |
| | Philip Sheridan, M.D., Clinical Team Leader |
| **Project Manager:** | Tina Chhabra |

## Table of Contents

## LIST OF TABLES



## LIST OF FIGURES

# 1 EXECUTIVE SUMMARY

In the pivotal study 1042-CDD-3001, the primary efficacy endpoint results are robust and the key secondary endpoints show numerical findings in favor of the efficacy of ganaxolone as (b) (4) treatment of seizures associated with Cyclin-dependent Kinase-like 5 Deficiency Disorder (CDD).

Specifically, for the primary endpoint of percent change from baseline in 28-day seizure frequency for major motor seizure types during the 17-week double-blind treatment phase, there was a statistically significant difference of -27.1% in the percent change in seizure frequency for subjects who received ganaxolone compared to subjects who received placebo. The results for this primary endpoint were robust and numerically favored the treatment of ganaxolone across subgroups.

The results of key secondary endpoints numerically favored the ganaxolone treatment group. There were higher proportions of subjects in the ganaxolone group with a $\geq$ 50% reduction from baseline in major motor seizure frequency, and higher proportions of parents/caregivers or clinicians of subjects in the ganaxolone group rated the response to treatment at the end of the 17-week double blind period as “Improved”. It was noted at the design stage that the trial was not powered to show statistical significance for these secondary endpoints.

# 2 INTRODUCTION

## 2.1 Overview

Ganaxolone is developed under IND 044020. Study 1042-CDD-3001 (referred to as Study 3001) is the single pivotal efficacy study to support the approval of ganaxolone for the treatment of seizures associated CDD. The study is a double-blind (DB), randomized, placebo-controlled study in patients aged 2 to 19 years. The primary endpoint is the percent change from baseline in 28-day major motor seizure frequency during the 17-week DB treatment phase. There are currently no approved medicinal products available specifically approved for the treatment of this disorder.

## 2.2 Data Sources

Materials reviewed for this application include the clinical study reports, raw and derived datasets, SAS codes used to generate the derived datasets and tables, protocols, statistical analysis plans, and documents of regulatory communications, which are located in the following directories: \\CDSESUB1\evsprod\NDA215904\0001.

# 3 STATISTICAL EVALUATION

## 3.1 Data and Analysis Quality

Documentation of statistical analysis methods was included with sufficient details for this reviewer to reproduce the applicant's key efficacy results.

There was a programming error that caused the eDiary to provide incorrect prompts of missing entries several days after they had in fact been entered by the parent or caregiver, who then re-recorded the seizure and medication information creating duplicate entries. The incorrect diary prompts affected patients in both arms of the study. The duplicate items were readily identifiable and were flagged as duplicate entries in the raw database. At the time of double-blind data lock (01 September 2020) a total of 1217 duplicate seizures were identified for 65 subjects (34 ganaxolone and 31 placebo) within the double-blind phase of the trial accounting for <2% of the seizures. There were a total 731 duplicate entries for 49 subjects that were different from the original entries, likely due to the entry from memory as most did not have a paper source. Therefore, the original data entry was considered the source and was included in the analysis dataset. This issue does not raise a major concern on the study integrity as the error was discovered and corrected prior to the database lock.

When preparing the NDA submission documents, the applicant discovered that the data in the 01 September 2020 data snapshot included duplicate seizure diary entries resulting from a data transfer error. This affected less than 2% of the over 73,000 total diary entries. As a result, another data snapshot took place on 19 May 2021 to remove the duplicate seizure diary entries. The study report was based on the latter data snapshot. However, evaluation is needed to

compare the results from the two data snapshots, as this correction occurred after data unblinding.

During the inspection conducted by the Agency, it was noticed that some of the seizure data were entered via proxy entry by study staff and the amount of proxy data entries did not seem trivial. After further evaluation, the proxy entries did not raise major concerns on the study integrity or have a significant impact on the study result. Additional details are in section 3.2.4.

## 3.2 Evaluation of Efficacy

### 3.2.1 Study Design and Endpoints

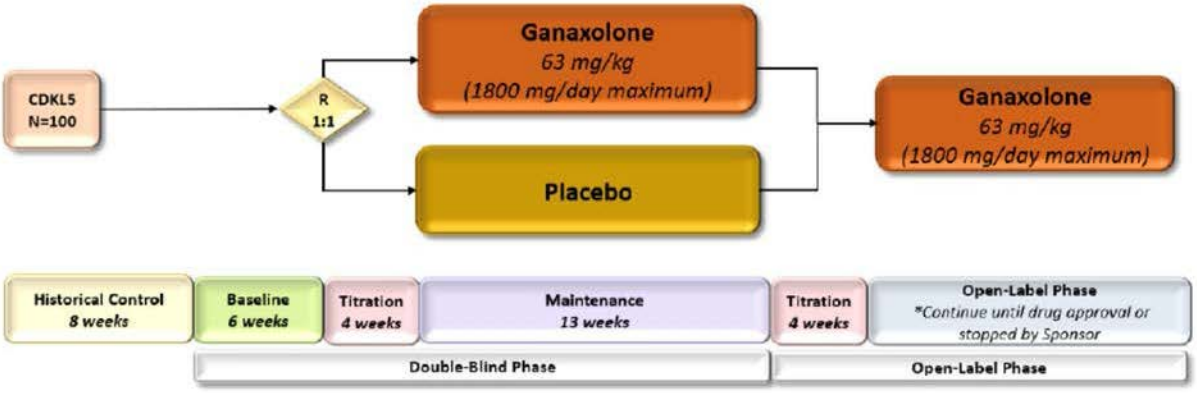
Study 3001 was initiated on June 30, 2018 and completed on July 31, 2020. The original protocol was issued on June 8, 2018 and the final protocol was dated July 26, 2020. The original SAP was dated August 22, 2019 and the final version is dated on May 18, 2021. The updates of SAP after the initial data lock on September 1, 2020 were minor.

There have been three analyses performed on the study data, a planned interim analysis (IA) for 52 subjects who completed the 17-week double-blind phase, a full analysis at double-blind database lock (data snapshot: 01 Sept 2020), and an updated analysis based on the updated data after correcting duplicate eDiary entries (data snapshot: 19 May 2021). This review describes the analysis results for the double-blind phase based on the updated data (data snapshot: 19 May 2021), unless otherwise specified. See additional detailed explanation in section 3.2.4.

***Study Design***
Study 1042-CDD-3001 was a phase 3 global, double-blind (DB), randomized, placebo-controlled trial of adjunctive ganaxolone treatment in children and young adults with CDD. The double-blind phase included 6 weeks prospective baseline, 4 weeks of titration followed by 13 weeks of dose maintenance. About 100 children and young adults aged 2-21 years (inclusive) with CDD were to be randomly assigned to receive ganaxolone or placebo (1:1 ratio) in addition to their standard anti-seizure treatment. The DB phase was followed by an open-label (OL) phase.

Participants were required to complete an electronic daily seizure calendar noting seizure type and frequency to determine ganaxolone's effect on drug resistant seizures. Subjects who discontinued investigational product treatment before the completion of the DB phase would continue to be followed per protocol and at minimum maintain daily seizure diary entry until the DB phase was completed. These subjects would return to the site 2 weeks after the taper for safety follow-up assessments.

**Figure 1. Schematic of Phase 3 Study Design**




***Efficacy Endpoint***

The primary endpoint was the percentage change from baseline in 28-day primary seizure frequency during the 17-week DB treatment phase. The term "primary seizures" was used in the protocol to refer to the seizure types evaluated for the primary endpoint; the more commonly accepted clinical term "major motor seizures" was used for those seizure types in the clinical study report (CSR). Major motor seizures include bilateral tonic (sustained motor activity ≥ 3 seconds), generalized tonic-clonic, bilateral clonic, atonic/drop or focal to bilateral tonic-clonic seizures.

The key secondary efficacy endpoints were as follows:

• Number (%) of subjects with a ≥50% reduction from baseline in primary seizure frequency.
• Clinical Global Impression of Improvement (CGI-I) at the last scheduled visit in the 17- week DB treatment phase.

*Reviewer's note: the protocol or SAP didn't specify whether the endpoint of CGI-I refers to CGI-I clinician or CGI-I caregiver. The CSR reported both as the key secondary endpoints.*

### 3.2.2 Statistical Methodologies

***Analysis Method***

The main efficacy analyses were based on the Intention-to-Treat (ITT) Population which comprised all randomized subjects who received at least one dose of study drug.

<u>Analyses of the primary efficacy endpoint</u>

The primary efficacy endpoint of percent change from baseline in 28-day seizure frequency was analyzed using the Wilcoxon Rank-Sum test. The primary analysis used all available data, even if they were collected after the subject stopped taking study medication, regardless of whether the subject took rescue medication.

For early drug termination prior to the end of the 17-week DB phase, caregivers were instructed to continue to provide daily seizure records until the end of the 17-week DB phase to prevent

missingness. Sensitivity analyses of the primary endpoint were performed for missing data due to subjects stopping recording measurements permanently (anticipated to be minimal in occurrence) prior to the end of the 17-week DB phase. In the first sensitivity analysis, the missing data were imputed using placebo data based on the corresponding quartile defined using that subject's available measurements during the baseline phase. The second sensitivity analysis assumed that subjects who stopped recording their seizure counts had higher seizure counts than the other subjects and imputed the missing data with the median of 5 highest placebo group counts.

Analyses of the secondary efficacy endpoints

Number (%) of subjects with a ≥50% reduction from baseline in major motor seizure frequency was analyzed using Fisher's Exact test.

CGI-I at the last scheduled visit in the 17-week DB treatment phase was analyzed using ordinal logistic regression. Proportional odds modelling was carried out by including treatment group as a factor.

***Interim Analyses***

Up to two formal interim analyses were planned on the primary endpoint. They were to be conducted when 50 subjects and 75 subjects were at least 17 weeks post randomization. O'Brien-Fleming boundaries would be used based on the actual number of subjects at the times of the interim analyses. The (one-sided) boundary was 0.0001 at the first IA and 0.0012 at the 2nd IA. The two-sided p-value at the final analysis would be approximately 0.048.

Due to unexpected increase in enrollment and all patients being randomized at the time when the first interim analysis was conducted, it was decided and agreed upon with the Data Monitoring Committee (DMC) that the second planned analysis was not necessary.

***Multiplicity Adjustment***

If the null hypothesis was rejected for the primary efficacy endpoint at the 2-sided α-level allocated to the final analysis of the primary endpoint, then statistical hypothesis testing would be performed on the 2 key secondary endpoints in the order listed in section 3.2.1.

*Reviewer's note: the SAP didn't explicitly specify the α-level for testing the key secondary endpoints. For group sequential design, the secondary endpoints cannot be tested at the full 2-sided 0.05 significance level without inflating the overall type I error.*

### 3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Of 101 subjects randomized, 95 (94.1%) completed the 17-week double-blind phase; 6 (5.9%) subjects discontinued from the study (2 subjects in the ganaxolone group and 4 subjects in the placebo group; Table 1).

**Table 1. Subject Disposition**

| Category | Placebo n (%) | Ganaxolone n (%) | Total n (%) |
|---|---|---|---|
| Randomized | 51 | 50 | 101 |
| ITT Population | 51 (100) | 50 (100) | 101 (100) |
| Subjects who Completed 17-week DB Phase | 47 (92.2) | 48 (96.0) | 95 (94.1) |
| Subjects who Completed 17-week DB Phase but Stopped Taking Study Drug Before the End | 0 | 3 (6.0) | 3 (3.0) |
| Reason for Discontinuation | | | |
| Adverse event | 4 (7.8) | 1 (2.0) | 5 (5.0) |
| Withdrawal by subject or parent/LAR | 0 | 1 (2.0) | 1 (1.0) |

Source: CSR Table 4.

The baseline demographic and disease characteristics were comparable between the two groups. Overall, majority of the study population was White (92%) and female (79%), and the mean age was 7.3 years at baseline. The median age at first seizure for all subjects was 2.0 months (range: 0 to 14 months). The median 28-Day major motor seizure frequency at baseline was 54 for subjects in the ganaxolone group and 49 for subjects in the placebo group (Table 2).

**Table 2. Baseline Demographic and Disease Characteristics**

| Characteristic | Placebo N = 51 | Ganaxolone N = 50 | Total N = 101 |
|---|---|---|---|
| Age(years) | | | |
| n | 51 | 50 | 101 |
| Mean (SD) | 7.73 (4.382) | 6.78 (4.705) | 7.26 (4.547) |
| Median | 7.00 | 5.00 | 6.00 |
| Q1, Q3 | 4.00, 11.00 | 3.00, 10.00 | 3.00, 10.00 |
| Min, Max | 2.0, 19.0 | 2.0, 19.0 | 2.0, 19.0 |
| Sex, n (%) | | | |
| Male | 10 (19.6) | 11 (22.0) | 21 (20.8) |
| Female | 41 (80.4) | 39 (78.0) | 80 (79.2) |
| Ethnicity, n (%) | | | |
| Hispanic or Latino | 6 (11.8) | 4 (8.0) | 10 (9.9) |
| Not-Hispanic or Latino | 43 (84.3) | 44 (88.0) | 87 (86.1) |
| Unknown | 1 (2.0) | 1 (2.0) | 2 (2.0) |
| Not reported | 1 (2.0) | 1 (2.0) | 2 (2.0) |
| Race, n (%) | | | |
| White | 47 (92.2) | 46 (92.0) | 93 (92.1) |
| Black or African American | 0 | 0 | 0 |
| Asian | 3 (5.9) | 2 (4.0) | 5 (5.0) |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Unknown | 0 | 0 | 0 |
| Not reported | 0 | 0 | 0 |
| Other | 1 (2.0) | 2 (4.0) | 3 (3.0) |
| Country | | | |
| Australia | 2 (3.9) | 4 (8.0) | 6 (5.9) |
| France | 3 (5.9) | 3 (6.0) | 6 (5.9) |
| Israel | 1 (2.0) | 0 | 1 (1.0) |
| Italy | 6 (11.8) | 9 (18.0) | 15 (14.9) |

| Characteristic | Placebo N = 51 | Ganaxolone N = 50 | Total N = 101 |
|---|---|---|---|
| Poland | 5 (9.8) | 5 (10.0) | 10 (9.9) |
| Russian Federation | 7 (13.7) | 7 (14.0) | 14 (13.9) |
| United Kingdom | 3 (5.9) | 4 (8.0) | 7 (6.9) |
| United States | 24 (47.1) | 18 (36.0) | 42 (41.6) |
| Age at first seizure (months) | | | |
| n | 51 | 50 | 101 |
| Mean (SD) | 2.3 (2.34) | 2.8 (2.70) | 2.6 (2.52) |
| Median | 2.0 | 2.0 | 2.0 |
| Q1, Q3 | 1.0, 2.0 | 1.0, 3.0 | 1.0, 3.0 |
| Min, Max | 0, 10 | 0, 14 | 0, 14 |
| Baseline 28-Day seizure frequency | | | |
| n | 51 | 49 | 100 |
| Mean (SD) | 104 (173.0) | 115 (138.4) | 110 (156.3) |
| Median | 49 | 54 | 50 |
| Q1, Q3 | 19, 120 | 31, 147 | 26, 142 |
| Min, Max | 0.7, 1021.3 | 5.5, 651.3 | 0.7, 1021.3 |

Source: FDA reviewer.

### 3.2.4 Results and Conclusions

*Analyses of the primary endpoint*

During the 17-week double-blind treatment phase, there was a statistically significant difference of -27.1% in the median percent change from baseline in seizure frequency (-30.7% for subjects in the ganaxolone group and -6.9% for the placebo group; p = 0.0036; Table 3). Note that 1 subject in the ganaxolone group had missing seizure data at baseline and was excluded from the analysis of the primary efficacy endpoint.

**Table 3. Summary of 28-Day Major Motor Seizure Frequency**

| | Placebo N = 51 | Ganaxolone N = 50 |
|---|---|---|
| Baseline | | |
| n | 51 | 49 |
| Median | 49.2 | 54.0 |
| Q1, Q3 | 18.7, 120.0 | 31.3, 147.3 |
| Double-Blind Phase | | |
| n | 51 | 50 |
| Median | 55.5 | 45.0 |
| Q1, Q3 | 21.6, 124.7 | 23.5, 106.3 |
| Percent Change from Baseline | | |
| n | 51 | 49 |
| Median | -6.9 | -30.7 |
| Q1, Q3 | -24.1, 39.7 | -49.5, -1.9 |
| Hodges-Lehmann Estimate of Location Shift (95% CI) | | -27.1 (-47.9, -9.5) |
| Wilcoxon Test p-value | | 0.0036 |

Source: CSR Table 8, confirmed by FDA reviewer.

The reviewer conducted a sensitivity analysis using an analysis of covariance (ANCOVA) that models log-transformed seizure frequency as a function of log-transformed baseline seizure frequency and treatment. The result showed a statistically significant reduction of 35.2% in seizure frequency with the treatment of ganaxolone (p-value=0.0084; Table 4), supporting the result of the primary analysis.

**Table 4. Sensitivity Analyses of 28-Day Seizure Frequency Using ANCOVA**

| | Placebo | Ganaxolone |
|---|---|---|
| N | 51 | 49 |
| Log seizure frequency during DB LSmean (SE) | 4.1 (0.12) | 3.6 (0.12) |
| Log Difference in LSMean (95% CI) | | -0.45 (-0.79, -0.12) |
| % reduction in seizure frequency compared to placebo | | 36.2% |
| ANCOVA p-value | | 0.0084 |

Source: FDA reviewer.

An IA was performed for 52 subjects who completed the 17-week double-blind phase. The p-value for the primary endpoint was 0.003, which didn't cross the O'Brien-Fleming boundary. The study continued to conduct the final analysis.

When preparing the NDA submission documents, the applicant discovered that the data included in the 01 September 2020 data snapshot and original CSR (submitted to IND 044020 on 18 January 2021) included duplicate seizure diary entries resulting from a data transfer error. This affected less than 2% of the over 73,000 total diary entries. The duplicate records were excluded in the updated data snapshot on 19 May 2021 data. The removal of these duplicate records resulted in minor differences between analysis results based on the 2 data snapshots. The previously reported analysis using the 01 September 2020 snapshot showed a seizure reduction from baseline of 32.2% for ganaxolone and 4.0% for placebo, with a p-value of 0.002 (results not shown in table).

*Assessment of the Impact of Missing data and Dropouts*

The amount of missing seizure data is small. Only 1 subject in each group had post baseline seizure data less than 4 weeks (i.e., no seizure data during maintenance phase), and 2 in each group had less than 8 weeks. The results of planned sensitivity analyses for missing data due to subjects stopping recording seizure permanently were similar to the results of the primary analysis (results not shown in table). The reviewer conducted a worst-case type of analysis in which the worst observed data (largest percent change from baseline) was used for subjects in ganaxolone group who dropped out during the treatment phase. The statistical significance of ganaxolone's treatment effect on seizure frequency still maintained (p-value=0.0158; Table 5).

**Table 5. Sensitivity Analysis of 28-Day Seizure Frequency for Handling Drop-outs**

| | Placebo | Ganaxolone |
|---|---|---|
| Percent Change from Baseline | | |
| n | 51 | 49 |
| Median | -6.9 | -28.1 |
| Q1, Q3 | -24.1, 39.7 | -43.5, 2.6 |
| Hodges-Lehmann Estimate of Location Shift (95% CI) | | -22.6 (-43.8, -5.6) |
| Wilcoxon Test p-value | | 0.0158 |

Source: FDA reviewer.

*Assessment of the Impact of Proxy Data Entries*

During the inspection conducted by the Agency, it was noticed that some of the seizure data were entered via proxy entry by study staff. The applicant responded to an information request that the total number of proxy data entries is 2695 (approximately 4%) for 38 subjects at 22 sites. These include proxy entry made by the site using the device and entry by the vendor into the e-diary database. The proxy entry was intended to provide a back-up plan if any unforeseen issues were encountered with the device (i.e., potential device malfunction, data sending issues and data unable to be recorded via devices). As the sources used to support the proxy entries were provided except for 6 data entries and the process of proxy data entry was documented, the reviewer does not consider it a major concern. Sensitivity analysis was conducted with proxy entries removed and the result was consistent with the primary analysis (Table 6).

**Table 6. Sensitivity Analysis of 28-Day Seizure Frequency Removing Proxy Entries**

| | Placebo | Ganaxolone |
|---|---|---|
| Percent Change from Baseline | | |
| n | 49 | 48 |
| Median | 0.51 | -29.42 |
| Q1, Q3 | -30.25, 32.10 | -57.29, -3.78 |
| Hodges-Lehmann Estimate of Location Shift (95% CI) | | -28.6 (-47.5, -9.9) |
| Wilcoxon Test p-value | | 0.0034 |

Source: Adapted from sponsor Table 27.2, confirmed by FDA reviewer.

*Analyses of the secondary endpoints*

The treatment difference in the number (%) of subjects with a ≥ 50% reduction from baseline in seizure frequency was not statistically significant (p = 0.0643; Table 7). The 50% response rate numerically favored the ganaxolone group (12 [24.5%] subjects in the ganaxolone group, 5 [9.8%] subjects in the placebo group). There was also a larger 25% response rate and 75% response rate in the ganaxolone group (Figure 2).

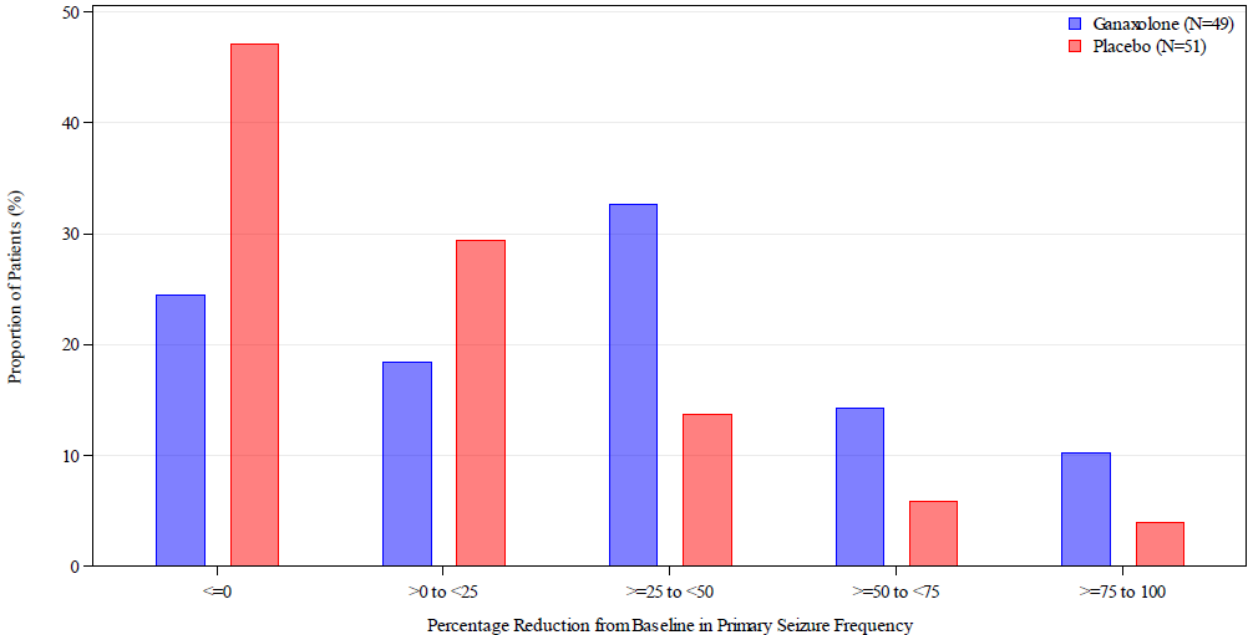
Although the SAP didn't specify whether the CGI-I endpoint refers to CGI-I clinician or CGI-I caregiver, neither endpoint achieved nominal statistical significance (nominal p = 0.0971 for the CGI-I (Parent/Caregiver) and 0.3518 for CGI-I (Clinician) scores). Numerically higher proportions of parents/caregivers or clinicians of subjects in the ganaxolone group rated the response to treatment at the end of the 17-week double blind period as "improved" compared to the placebo group (Table 7).

**Table 7. Summary of Secondary Endpoints**

| Variable | Placebo | Ganaxolone |
|---|---|---|
| Response Rate, N | 51 | 49 |
| n (%) | 5 (9.8) | 12 (24.5) |
| Difference (95% CI) | | 14.7 (-4.7, 33.8) |
| Fisher's Exact test p-value | | 0.0643 |
| CGI-I (Parent/Caregiver), N | 48 | 48 |
| Very Much Improved, n (%) | 1 (2.1) | 0 |
| Much Improved, n (%) | 7 (14.6) | 13 (27.1) |
| Minimally Improved, n (%) | 13 (27.1) | 17 (35.4) |
| No Change, n (%) | 22 (45.8) | 14 (29.2) |
| Minimally Worse, n (%) | 4 (8.3) | 2 (4.2) |
| Much Worse, n (%) | 1 (2.1) | 2 (4.2) |
| Very Much Worse, n (%) | 0 | 0 |
| Odds Ratio (95% CI) | | 1.87 (0.89, 3.91) |
| Logistic Regression p-value | 9 | 0.0971 |
| CGI-I (Clinician), N | 48 | 48 |
| Very Much Improved, n (%) | 0 | 0 |
| Much Improved, n (%) | 7 (14.6) | 7 (14.6) |
| Minimally Improved, n (%) | 13 (27.1) | 19 (39.6) |
| No Change, n (%) | 19 (39.6) | 16 (33.3) |
| Minimally Worse, n (%) | 9 (18.8) | 2 (4.2) |
| Much Worse, n (%) | 0 | 3 (6.3) |
| Very Much Worse, n (%) | 0 | 1 (2.1) |
| Odds Ratio (95% CI) | | 1.41 (0.68, 2.94) |
| Logistic Regression p-value | | 0.3518 |

Source: CSR Table 11, confirmed by the reviewer.

**Figure 2. Proportion of Patients by Category of Percent Reduction in 28-Day Seizure Frequency**




Source: CSR Figure 14.2.4

## 3.3 Evaluation of Safety

Please see the clinical review.

# 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

## 4.1 Gender, Race, Age, and Geographic Region

The results of subgroup analyses for the primary endpoint were in Table 8. Subgroups of race were not included as majority of the subjects were White and the number of subjects of other races was limited. There appeared to have a treatment effect on seizure frequency favoring Ganaxolone across the subgroups of age, gender, and geographical regions.

**Table 8. Summary of Percent Change in Seizure Frequency by Demographics Subgroups**

| | Placebo | | Ganaxolone | | Ganaxolone vs. Placebo | |
|---|---|---|---|---|---|---|
| | N | Median % change | N | Median % change | Treatment difference | 95% CI |
| Age | | | | | | |
| <7 years | 22 | -9.0% | 29 | -30.7% | -27.0% | (-63.2, 4.4) |
| >=7 years | 29 | -1.5% | 20 | -30.1% | -31.1% | (-56.2, -9.4) |
| Gender | | | | | | |
| Male | 10 | 7.4% | 11 | -32.0% | -42.1% | (-95.2, -8.4) |
| Female | 41 | -10.2% | 38 | -27.5% | -22.2% | (-48.4, -1.4) |
| Geographical Region | | | | | | |
| USA | 24 | 2.2% | 17 | -32.0% | -34.2% | (-65.1, -7.2) |
| Rest of World | 27 | -11.6% | 32 | -27.5% | -19.7% | (-53.1, 4.5) |

Source: FDA reviewer.

## 4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

# 5 SUMMARY AND CONCLUSIONS

## 5.1 Statistical Issues

The pivotal study 3001 was a group sequential study evaluating the efficacy and safety of Ganaxolone versus placebo, with percentage change in major motor seizure frequency over a 17-week treatment period as the primary endpoint. The study specified 2 key secondary endpoints. However, it was not clear whether the key secondary endpoint of CGI-I refers to CGI-I clinician or CGI-I caregiver.

A hierarchical testing strategy was specified starting with the primary endpoint tested at approximately 0.048 in the final analysis per O'Brien-Fleming boundary. However, the SAP didn't explicitly specify the α-level for testing the key secondary endpoints. For group sequential design, the secondary endpoints cannot be tested at the full 2-sided 0.05 significance level. As only the primary endpoint and none of the key secondary endpoints reached nominal statistical significance, further discussion on multiplicity adjustment was not needed.

The result of the primary endpoint was robust and the secondary endpoints all numerically favored ganaxolone. Based on the Type C meeting minutes on 12/19/2017, “this single primary endpoint will determine if the trial indicates efficacy or not. A limited number of secondary endpoints are welcome, but are not needed to “bolster” the primary efficacy endpoint.” It was also pointed out that “the nonseizure secondary endpoints will be of interest but, due to the power limitations of this small patient population, the trial will not be powered to give these secondary endpoints statistical significance.”

## 5.2 Collective Evidence

As there was a single pivotal study, a summary of the collective evidence of effectiveness was not applicable.

## 5.3 Conclusions and Recommendations

In this trial, the primary efficacy endpoint results are robust. The key secondary endpoints show numerical findings in favor of the efficacy of ganaxolone as (b) (4) treatment of seizures associated with CDD.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# Statistical Review and Evaluation

CLINICAL STUDIES

| | |
|---|---|
| **NDA/Serial Number:** | 215904/0001 |
| **Drug Name:** | Ztalmy (ganaxolone) 50 mg/ml oral suspension |
| **Indication(s):** | Treatment of cyclin-dependent, kinase-like 5 (CDKL5) deficiency disorder |
| **Applicant:** | Marinus Therapeutics, Inc |
| **Date(s):** | Date of Document: 7/22/2021<br>Consult received date: 9/29/2021<br>Completion date: 11/20/2021<br>Revised on 2/8/2022 |
| **Review Priority:** | Priority review |
| **Biometrics Division:** | Division of Biometrics VI |
| **Statistical Reviewer:** | Wei Liu, Ph.D., DBVI/OB |
| **Concurring Reviewers:** | Qianyu Dang, Ph.D., Team Leader, DBVI/OB<br>Yi Tsong, Ph.D., Division Director, DBVI/OB/OTS |
| **Medical Division:** | Division of Neurology 2 (DN2) and Controlled Substance Staff (CSS) |
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| **Keywords:** NDA review, clinical studies, Crossover design; Self-reported endpoint; Multiple endpoints; human drug abuse study | |

# Table of Contents

## LIST OF TABLES



## LIST OF FIGURES

## 1. EXECUTIVE SUMMARY

The applicant, Marinus Therapeutics, Inc, submitted the data of Study 1042-HAP-1001 in NDA 215904 for the assessment of abuse potential of Ganaxolone. The Study 1042-HAP-1001 was a single-center, randomized, double-blind, double-dummy, placebo- and active-controlled, 5-way crossover study to evaluate the abuse potential of single oral doses of ganaxolone compared with single oral doses of lorazepam and placebo in healthy, male and female, non-dependent, recreational CNS depressant users. A total of 46 subjects were randomized into the treatment phase and 44 subjects completed the study.

The primary endpoint of Study 1042-HAP-1001 was the maximum (peak) effect (Emax) for Drug Liking ("at this moment"), assessed on bipolar (0–100 point) visual analog scales (VAS). The secondary endpoints included the VAS Emax of Overall Drug Liking, Take Drug Again, High, Good Drug Effects, Bad Drug Effects, Any Drug Effects.

This reviewer analyzed the data of completers population and concluded the following:

1. the validation test for comparing the mean Drug Liking VAS Emax between Lorazepam 6 mg and placebo was statistically significant; the lower 95% confidence limit (one-sided) of the mean difference was greater than the test margin of 15 points.
2. for the relative abuse potential of Ganaxolone, the mean Emax of Drug Liking VAS to the treatment of Lorazepam 6 mg was statistically significantly greater than that of each Ganaxolone dose (400 mg, 800 mg, ang 2000 mg), suggesting that Ganaxolone at above doses was less liked than Lorazepam 6 mg at a level of 0.05 (one-sided) in healthy, male and female, non-dependent, recreational CNS depressant users.
3. for the absolute abuse potential of Ganaxolone, the null hypothesis of the mean Emax of Drug Liking VAS to Ganaxolone response being at least 11 points higher than that of placebo was rejected for the dose 400 mg and dose 800 mg, respectively, suggesting that drug liking of Ganaxolone at the two low doses was not significantly different from that of placebo. However, there was no sufficient evident to reject the null hypothesis for Ganaxolone 2000 mg – placebo because of the upper 95% confidence limit greater than 11, suggesting that Ganaxolone 2000 mg may have abuse potential.

The results of the primary analysis were supported by the analysis of key secondary endpoints. Additional supportive results come from the consistent positive dose response in the mean Emax of the primary and key secondary endpoints.

**Summary of The Primary Analysis for Evaluating the Drug Abuse Potential of Ganaxolone (Completers, n=44).**

| | | | | 95% CI* | | 95% CI** | |
|---|---|---|---|---|---|---|---|
| **Hypothesis Testing** | **Mean diff** | **SE** | **p-value** | **LCL** | **UCL** | **LCL** | **UCL** |
| Study validation, $H_o$: $\mu_C - \mu_P \leq 15$ vs. $H_a$: $\mu_C - \mu_P > 15$ | | | | | | | |
| Lorazepam 6 mg – Pcb | 22.7 | 2.66 | 0.0029 | 18.3 | Inf | 17.4 | 28.1 |
| Relative abuse potential, $H_o$: $\mu_C - \mu_T \leq 0$ vs. $H_a$: $\mu_C - \mu_T > 0$ | | | | | | | |
| Lorazepam 6 mg - Ganaxolone 400 mg | 18.1 | 2.3 | <0.0001 | 14.3 | Inf | 13.5 | 22.8 |
| Lorazepam 6 mg - Ganaxolone 800 mg | 17.0 | 2.7 | <0.0001 | 12.5 | Inf | 11.6 | 22.3 |
| Lorazepam 6 mg - Ganaxolone 2000 mg | 13.0 | 2.16 | 0.0000 | 9.3 | Inf | 8.6 | 17.3 |
| Absolute abuse potential, $H_o$: $\mu_T - \mu_P \geq 11$ vs. $H_a$: $\mu_T - \mu_P < 11$ | | | | | | | |
| Ganaxolone 400 mg - Pcb | 4.6 | 2.51 | 0.0072 | -Inf | 8.8 | -0.5 | 9.7 |
| Ganaxolone 800 mg - Pcb | 5.8 | 2.33 | 0.0152 | -Inf | 9.7 | 1.1 | 10.5 |
| Ganaxolone 2000 mg - Pcb | 9.8 | 2.71 | 0.3235 | -Inf | 14.3 | 4.3 | 15.2 |

Note: Analyses were carried out in the Completers population using paired t-test.
p-value was one-sided at alpha=0.05.
LCL: lower confidence limit, UCL: upper confidence limit. Pcb: Placebo.
* one-sided test; ** two-sided test.

## 2. INTRODUCTION

### 2.1 Overview

Ganaxolone (3α-hydroxy-3β-methyl-5α-pregnan-20-one) is a methyl analog of the endogenous neurosteroid allopregnanolone that allosterically modulates GABAA receptors in the CNS at sites that are distinct from other allosteric GABAA receptor modulators. Ganaxolone has similar pharmacological activity as allopregnanolone, including potent antiepileptic, anxiolytic, sedative, and hypnotic effects in animals.

This study was a single-center, randomized, double-blind, double-dummy, placebo- and active-controlled, 5-way crossover study to evaluate the abuse potential of single oral doses of ganaxolone compared with single oral doses of lorazepam and placebo in healthy, male and female, non-dependent, recreational CNS depressant users. Ganaxalone is proposed for the treatment of cyclin-dependent, kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients aged 2 years and older.

### 2.2 Data Source

| | |
|---|---|
| **Application:** | NDA215904 |
| **Company** | Marinus Therapeutics, Inc. |
| **Drug** | Ganaxolone |
| **CDER EDR link** | file://CDSESUB1/evsprod/NDA215904/0001 |
| **Letter date** | 7/20/2021 |

After the statistical consult was received, we found that the sponsor did not submit the pharmacodynamic dataset in the original submission. Therefore, we sent the following Information Request to the sponsor on October 14, 2021:

> *We are not able to locate the pharmacodynamic dataset of NDA215904 Study 1042 -HAP-1001 for the analysis of the primary and secondary endpoints (such as Emax, Emin, TEmax, and TA_AUE for Drug Liking, Overall Drug Liking, High, Take Drug Again, Good Drug Effects, Bad Drug Effects, Any Drug Effects, etc.). If the data were not submitted, please submit the dataset containing all variables in the models pre-specified in your study protocol including (but not limited to)*
>
> - *Sequence (For example, XYZACBDFE)*
> - *Period (numeric)*
> - *TRTP (Treatment name, Placebo, Lorazepam 6 mg, Ganaxolone 400 mg, etc.)*
> - *TRTN (treatment number, numerical)*
> - *Complfl (Flag for completers)*
> - *first-order carryover effect*
> - *VAS assessment time points (in hour) in each treatment period*
>
> *Please also submit the define.pdf document regarding this dataset.*

The sponsor submitted the analysis dataset on 10/19/2021.

## 3. REVIEW REPORT on STUDY 1042-HAP-0101

### 3.1 STUDY OBJECTIVES

*Primary Objective*

To evaluate the abuse potential of single oral doses of ganaxolone relative to lorazepam and placebo in healthy, non-dependent, recreational CNS depressant users.

*Secondary Objectives*

- To assess the PK of single oral doses of ganaxolone in healthy, non-dependent, recreational CNS depressant users.
- To assess the safety and tolerability of single oral doses of ganaxolone in healthy, non-dependent, recreational CNS depressant users.

### 3.2 STUDY DESIGN

This was a single-center, randomized, double-blind, double-dummy, placebo- and active-controlled, 5-way crossover study to evaluate the abuse potential of single oral doses of ganaxolone compared with single oral doses of lorazepam and placebo in healthy, male and female, non-dependent, recreational CNS depressant users. The study consisted of 2 parts: Dose Selection (Part A) and the Main Study (Part B). Dose Selection comprised 3 phases: Screening, Dose Escalation, and Follow-up. The Main Study consisted of 4 phases: Screening, Qualification, Treatment, and Follow-up.

In the Main Study (Part B), after a screening period of up to 28 days, subjects were admitted to the clinical site on the day before first study drug administration in the Qualification Phase (Day -1). During the Qualification Phase, subjects received lorazepam 6 mg (active control, scheduled IV drug) and placebo in a crossover manner, under fed conditions, to ensure they were able to discriminate the positive effects of the active control and to demonstrate that they were able to tolerate the administered dose. The two treatments in the Qualification Phase were denoted as:

- Treatment X – Lorazepam 6 mg: 3 × 2 mg lorazepam tablets encapsulated into 1 capsule
- Treatment Y – Placebo: 1 × placebo capsule

Subjects were required to meet the following criteria to be considered eligible for enrollment in the Treatment Phase of the Main Study (Part B):

1. Peak score in response to lorazepam 6 mg greater than that of placebo on the bipolar Drug Liking VAS (difference of at least 15 points), with peak score of at least 65 points for lorazepam.
2. Acceptable placebo response based on Drug Liking VAS (score between 40 and 60 points, inclusive).
3. Acceptable overall responses to lorazepam and placebo on the subjective measures, as judged by the investigator or designee.
4. Able to tolerate the 6 mg dose of lorazepam, as judged by an investigator, including no episodes of vomiting during the first 3 hours post-dose. Subjects with unarousable sedation

within the first 4 hours post-dose were not eligible for the Treatment Phase (based on the MOAA/S).

5. General behavior suggested that the subject could successfully complete the study, as judged by the investigational site staff.

Study drug administration in the Qualification Phase was separated by approximately 24 hours. Subjects were discharged from the clinical site on Day 3, at least 24 hours after the last study drug administration. The washout interval between last study drug administration in the Qualification Phase and first study drug administration in the Treatment Phase was at least 3 days.

Eligible subjects were admitted back to the clinical site for the Treatment Phase on Day -1 prior to the first study drug administration. Subjects were randomized to 1 of 10 sequences (two 5 × 5 Williams squares) in the Treatment Phase, where they received the following 5 orally administered treatments, under fed conditions, in a randomized crossover manner:

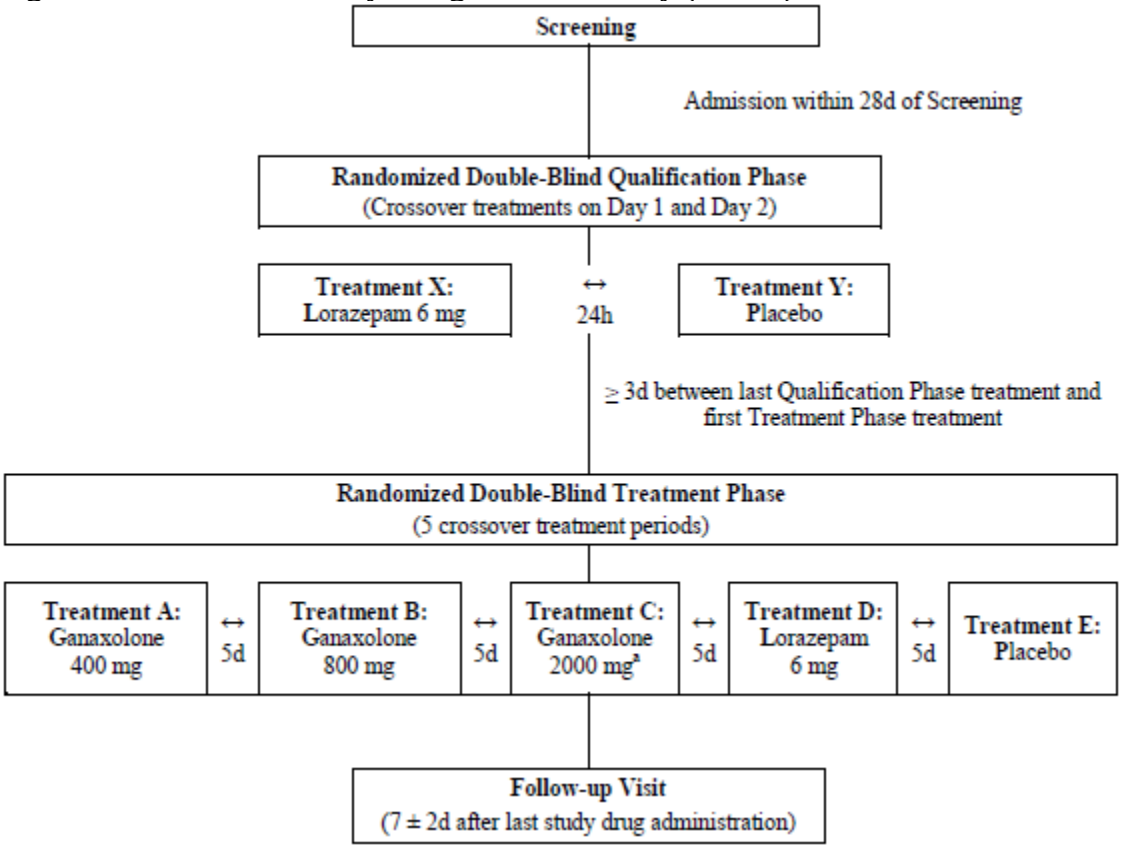
- Treatment A: Ganaxolone 400 mg
- Treatment B: Ganaxolone 800 mg
- Treatment C: Ganaxolone 2000 mg*
- Treatment D: Lorazepam 6 mg
- Treatment E: Placebo

** The highest ganaxolone dose planned in the protocol was originally set at 1600 mg; however, based on data from Part A, 2000 mg ganaxolone was considered to be an appropriate high dose for the Main Study.*

Each study drug administration was separated by 5 days. Subjects remained housed at the clinical site for the duration of Treatment Phase and were discharged after completion of the 24-hour assessments following the last study drug administration in Treatment Period 5. A follow-up visit occurred 7 days (± 2 days) after the last study drug administration or early discontinuation.

An overview of the study design (Part B) is presented in Figure 1.

**Figure 1. Overview of Study Design – Main Study (Part B)**




d = day
a Ganaxolone doses planned in the protocol were 400, 800, and 1600 mg; however, based on data from Dose Selection (Part A), 2000 mg ganaxolone was considered the appropriate high dose for the Main Study.
Note: The sequence of treatments shown is for illustration of the overall design and does not necessarily represent an actual treatment sequence.

## 3.3 PHARMACODYNAMIC ENDPOINTS

*Primary endpoint*

The Emax(0-8h) on the bipolar "at this moment" Drug Liking VAS was the primary PD endpoint in the Main Study (Part B).

*Secondary endpoints*

The key secondary PD endpoints in Part B were:

- Overall Drug Liking VAS (Emax)
- Take Drug Again VAS (Emax)

The other secondary PD endpoints in Part B were as follows:

- Balance of effects:

– Drug Liking VAS (Emin, TEmax(0-8h)/TEmin and AUE(0-8h))

– Overall Drug Liking VAS (Emin)

– Take Drug Again VAS (Emin)

- Positive effects:

– Good Effects VAS (Emax, TEmax, and AUE(0-8h))

– High VAS (Emax, TEmax, and AUE(0-8h))

- Negative effects:

– Bad Effects VAS (Emax, TEmax, and AUE(0-8h))

- Other subjective effects:

– Alertness/Drowsiness VAS (Emin, TEmin, and AOE(0-8h))

– Any Effects VAS (Emax, TEmax, and AUE(0-8h))

– Drug Similarity VAS (12-hour score)

- Cognitive/psychomotor effects and observer assessments:

– RTI 5-Choice Reaction Time (referred to as Reaction Time; Emax, CFBmax, and AUE(0-8h))

– RTI 5-Choice Movement Time (referred to as Movement Time; Emax, CFBmax, and AUE(0-8h))

– RTI Total Error Score (Emax, CFBmax, and AUE(0-8h))

– PAL Total Errors (Adjusted) (Emax, CFBmax, and AUE(0-8h))

– PAL First-Attempt Memory Score (Emin, CFBmin, and AOE(0-8h))

– PAL Total Attempts (Emax, CFBmax, and AUE(0-8h))

– MOAA/S (Emin, CFBmin, and AOE(0-8h))

## 3.4 Statistical Methodologies of the Sponsor

### *3.4.1 Sample Size Determination (Part B)*

Assuming a drop-out rate of approximately 20%, approximately 50 subjects was planned for randomization into the Treatment Phase in order to achieve a minimum of 40 completers (at least 1 subject per treatment sequence). It was assumed that the true mean difference between lorazepam and placebo for the primary endpoint was approximately 23.1 points, and that within-subject SD of the paired differences was approximately 16.5 points (Schoedel et al., 2011). It was estimated that a sample size of 40 completed subjects would provide at least 80% power to detect a mean difference in Drug Liking VAS Emax(0-8h) between lorazepam and placebo, with a margin of 15 points ($\delta 1$) in a 1-sided test at a 5% level of significance.

### *3.4.2 Analysis population:*

- Randomized Population: All subjects who were assigned a randomization number in the Treatment Phase.
- Completer Population: All randomized subjects who completed all treatment periods in the Treatment Phase and who had at least 1 Drug Liking VAS observation within 2 hours of Tmax for each treatment in the Treatment Phase.

*Review's comment: We have recently recommended the use of modified completer population (MCP).*

*3.4.3 Statistical Analysis Plan*

Pharmacodynamic data were analyzed for the Completer Population as the primary analysis. A supplemental analysis using the primary endpoint (Drug Liking VAS Emax(0-8h)) may have been performed using the Per Protocol Population, if the size of this population was substantially different from the Completer Population.

A mixed-effects model for a crossover study design was used to compare the primary and secondary PD endpoints between treatments (e.g., Emax(0-8h) or Emax, Emin, AUE(0-8h), AOE(0-8h), CFBmax, and CFBmin) with appropriate covariance-variance structure, if the residuals were normally distributed. The model included treatment, period, sequence and first-order carryover effect as fixed effects, and subject as a random effect. Baseline (pre-dose) was to have been included as a covariate (where applicable).

After it was determined if the treatment variance was homogeneous or heterogeneous, the residuals from each mixed-effect model were investigated for normality using the Shapiro-Wilk W test. The null and alternative hypotheses for this analysis are shown below:

$H_0$: Distribution of residuals is normal

$H_a$: Distribution of residuals is not normal

If the residuals from the mixed-effect model were normally distributed (e.g., *P* value $\geq 0.05$) it was to be determined if carryover effects were to have been included.

Carryover effects were defined as the treatment administered in the previous treatment period. As there were no carryover effects in Treatment Period 1, placebo was used in this period. If the carryover effect was found to be non-significant at alpha $\geq 0.25$, then the term was to have been dropped from the analysis model. If the carryover effect was found to be significant at the alpha = 0.25, it was to have been included in the model.

The conditional residuals from the mixed-effects model were investigated for normality using the Shapiro-Wilk W test. If the normality assumption of the model was satisfied, least squares means, SE, and 1-sided 95% or 2-sided 90% CIs for treatments and treatment differences were derived from the mixed-effect model. *P* values were provided for the effects and the contrasts.

*Reviewer's comments: The confidence interval cannot always be used for making a conclusion for a statistical test, especially the Sign test and the distribution free CI are two different methodologies. The conclusion of a comparison should be based on the Sign test.*

If the normality assumption of the model was not satisfied for a PD endpoint, the Friedman's test was used to test the overall treatment effect. The distribution of the paired difference for each contrast was examined in terms of normality and skewness. Each paired difference was investigated for normality using the Shapiro-Wilk W-test. If the *P* value for the distribution of the paired difference was normal, that is, *P* value $\geq 0.05$, a paired t-test was used.

If the paired difference was not normally distributed, that is, *P* value $< 0.05$, the following steps were taken to test skewness:

a) If the hypothesis was upper-tailed, and skewness was (0, 0.5), then mean difference, SE, 1-sided 95% CI and *P* value from the t-test were output.

b) If the hypothesis was upper-tailed, and skewness < 0 or skewness > 0.5 then median of the paired difference (Q1-Q3), 1-sided 95% CI, and *P* value from the sign test were output.

c) If the hypothesis was lower-tailed, and skewness was (-0.5, 0) then mean difference, SE, 1-sided 95% CI and *P* value from the t-test were output.

d) If the hypothesis was lower-tailed, and skewness < -0.5 or skewness > 0 then median of the paired difference (Q1-Q3), 1-sided 95% CI and *P* value from the sign test were output.

e) If the hypothesis was 2-tailed, and skewness was (-0.5, 0.5), then mean difference, SE, 2-sided 90% CI and *P* value from the t-test were output.

f) If the hypothesis was 2-tailed, and skewness < -0.5 or skewness > 0.5, then median of the paired difference (Q1-Q3), 2-sided 90% CI, and *P* value from the sign test were output.

*3.4.4 Hypothesis testing*

Primary Endpoint Analysis

The 1-sided p-values ($\alpha$=0.05) and 2-sided 90% CIs of the mean differences for Drug Liking VAS Emax(0-8h) were presented based on the following 3 primary hypotheses, to be tested sequentially:

1. The positive control (C), lorazepam, produces responses that show greater abuse potential, by more than 15 points, compared to placebo (P):

$$H_o: \mu_c - \mu_p \leq 15 \text{ vs. } H_a: \mu_c - \mu_p > 15 \quad (1)$$

2. The test drug (T), ganaxolone, produces responses that show less abuse potential compared to positive control, lorazepam (C):

$$H_o: \mu_c - \mu_t \leq 0 \text{ vs. } H_a: \mu_c - \mu_t > 0 \quad (2)$$

3. The test drug (T), ganaxolone, produces responses that show similar abuse potential compared to placebo (P), where “similar” is defined as a difference of less than 11 points:

$$H_o: \mu_t - \mu_p \geq 11 \text{ vs. } H_a: \mu_t - \mu_p < 11 \quad (3)$$

Statistical significance at the 1-sided 0.05 level should have been achieved for all 3 hypotheses; further, for hypotheses #2 and #3, statistical significance at the 1-sided 0.05 level should have been achieved for all doses of ganaxolone.

A pre-specified sensitivity analysis may have been performed if the criterion for validity of more than 15 points was not met. The sensitivity analysis would exclude subjects who showed a similar response to all treatments (i.e., ≤ 5-point difference in Drug Liking VAS Emax(0-8h) between all 5 treatments) or who showed inappropriate responses to placebo relative to the positive control (i.e., Emax(0-8h) for placebo > 60 and Emax(0-8h) for placebo > Emax(0-8h) for lorazepam by ≥ 5 points). Because validity criteria were met for the primary analysis, this sensitivity analysis was not performed.

*Review’s comment: This sensitive analysis uses MCP.*

The secondary PD endpoints for the Treatment Phase (e.g., Emax or Emax(0-8h), Emin, AUE(0-8h), AOE(0-8h), CFBmax, and CFBmin) were also analyzed using a mixed-effect model for a crossover study, a paired t-test, or a non-parametric approach (where appropriate) through the process explained above. No specific margins were selected for key or other secondary endpoints as there was no medical literature to support selection of such margins for endpoints other than Drug Liking VAS Emax(0-8h).

The following comparisons for secondary endpoints (excluding Emin) were evaluated from 1-sided 95% CIs ($\alpha$=0.05) using the confirmatory type of hypothesis as shown below:

- Lorazepam (C) vs. placebo (P): $H_0$: $\mu_C - \mu_P \leq 0$ vs. $H_a$: $\mu_C - \mu_P > 0$
- Lorazepam (C) vs. each dose of ganaxolone (T): $H_0$: $\mu_C - \mu_T \leq 0$ vs. $H_a$: $\mu_C - \mu_T > 0$

The Emin endpoints were evaluated from 1-sided 95% CIs ($\alpha$=0.05) using the confirmatory type of hypothesis as shown below:

- Lorazepam (C) vs. placebo (P): $H_0$: $\mu_C - \mu_P \geq 0$ vs. $H_a$: $\mu_C - \mu_P < 0$
- Lorazepam (C) vs. each dose of ganaxolone (T): $H_0$: $\mu_C - \mu_T \geq 0$ vs. $H_a$: $\mu_C - \mu_T < 0$

Comparisons for secondary endpoints between ganaxolone and placebo were evaluated from 2-sided 90% confidence intervals ($\alpha$=0.10) using the confirmatory type of hypothesis as shown below:

- Each dose of ganaxolone (T) vs. placebo (P): $H_0$: $\mu_T - \mu_P = 0$ vs. $H_a$: $\mu_T - \mu_P \neq 0$

### 3.5 Disposition of Subjects (Part B)

Of the 46 subjects randomized in the Treatment Phase, 46 subjects (100.0%) received at least 1 dose of study drug and were included in the Safety Population, while 44 subjects (95.7%) completed the study. Two subjects (4.3%) discontinued after Treatment Period 3 (1 subject after receiving 2000 mg ganaxolone, the other following 6 mg lorazepam) due to home or family emergencies as summarized in Table 1.

**Table 1. Summary of Subject Disposition in the Main Study (Part B)**

| | Overall n (%) |
|---|---|
| Number of subjects in the Randomized Population | 46 |
| Subjects who received at least 1 dose (Safety Population) | 46 (100.0) |
| Subjects who completed the study | 44 (95.7) |
| Subjects who discontinued | 2 (4.3) |
| Primary reason for discontinuation | |
| Home/family emergency | 2 (4.3) |

Note: Percentages were calculated based on the number of subjects randomized in the Randomized Population.

Source: Table 10 in 1042-HAP-1001-study-report.pdf

### 3.6 Sponsor's Summary and Conclusions

**Primary Endpoint (Drug Liking VAS Emax(0-8h))**

The first primary hypothesis of study validity was met; the positive control, lorazepam 6 mg, produced responses that showed greater abuse potential, by more than 15 points, on Drug Liking VAS Emax(0-8h) (lower CI limit of the 1-sided 95% CI of 20.0; P = 0.0069), compared to placebo. Thus, it can be concluded that the study was valid.

The second primary hypothesis, that ganaxolone has less abuse potential than lorazepam, was met for all 3 doses of ganaxolone. The lower limits of the 1-sided 95% CIs for the comparisons of lorazepam 6 mg with ganaxolone on Drug Liking VAS Emax(0-8h) were 14.3, 12.5, and 8.0 for ganaxolone 400, 800, and 2000 mg, respectively (all $P < 0.0001$). Therefore, it can be concluded that ganaxolone has less abuse potential than lorazepam.

For the third primary hypothesis (absolute abuse potential), ganaxolone 400 mg produced responses that showed similar abuse potential compared to placebo (i.e., difference in Drug Liking VAS Emax(0-8h) < 11 points; upper CI limit of 8.8; $P = 0.0072$); however, ganaxolone 800 and 2000 mg each produced responses that could not be considered similar to those of placebo (upper CI limits of 17.0 [$P = 0.5000$] and 19.0 [$P = 0.6864$], respectively). Thus, because the hypothesis must be met for all 3 doses of ganaxolone, it cannot be concluded that ganaxolone has abuse potential similar to that of placebo.

**Secondary Subjective Endpoints**

Lorazepam 6 mg demonstrated significantly greater effects compared to placebo on the key secondary endpoints of Overall Drug Liking VAS Emax and Take Drug Again VAS Emax, as well as all positive (Good Effects, High VAS), sedative (Alertness/Drowsiness VAS) and other subjective effects (Any Effects VAS) endpoints. Lorazepam 6 mg also showed small but statistically significant differences from placebo in negative effects (Bad Effects VAS). Based on the Drug Similarity VAS, subjects rated lorazepam 6 mg as similar to "benzodiazepines," and to a lesser extent "opioids," but not similar to other drug classes. Subjective effects of lorazepam generally peaked between 2 and 3 hours post-dose and lasted for at least 12 hours post-dose.

Lorazepam showed significantly greater effects compared to all 3 ganaxolone doses on all secondary subjective endpoints.

Ganaxolone 400 mg was not significantly different from placebo on key secondary endpoints (Overall Drug Liking VAS Emax and Take Drug Again VAS Emax), but did show significantly greater positive, sedative, and other effects compared to placebo. Ganaxolone 800 and 2000 mg showed significantly greater effects compared to placebo on the key secondary endpoints, as well as measures of positive, sedative, and other drug effects. Ganaxolone was not associated with significant negative effects at any dose level. "Benzodiazepine" similarity ratings were higher with ganaxolone compared to placebo, but lower than those of lorazepam 6 mg. Subjective effects with ganaxolone peaked between 1 to 3 hours post-dose, but were generally transient, lasting only approximately 6 hours post-dose.

**Secondary Cognitive/Psychomotor Endpoints**
Lorazepam 6 mg was associated with significant cognitive and psychomotor impairment compared to placebo across RTI and PAL endpoints, with the exception of with PAL Total Attempts, demonstrating the expected decrements in reaction times, processing speed, attention, and episodic memory (i.e., amnestic effects). Impairment generally peaked at 3 hours post-dose and lasted for up to 12 hours post-dose.

Impairment with lorazepam 6 mg was also significantly greater compared to all 3 ganaxolone doses across cognitive and psychomotor endpoints.
Ganaxolone, however, was not associated with impairments in episodic memory on any of the PAL endpoints. Sporadic statistical differences were seen on a few RTI CFBmax endpoints (Reaction Time at 400 mg; Movement Time and Total Error Score at 2000 mg); however, the magnitude of differences was markedly smaller compared to those observed with lorazepam 6 mg.

**Overall Pharmacodynamic Conclusions**
In this valid study, ganaxolone showed less abuse potential compared to lorazepam on the primary and secondary endpoints and greater abuse potential compared to placebo. Effects of ganaxolone on cognitive or motor impairment were small, sporadic, and markedly lower than those of lorazepam.

## 3.7 Reviewer's Assessment

The statistical analysis of this reviewer used the completer population.

*3.7.1 Descriptive Analysis*

The mean time course profiles by treatment for Drug Liking VAS, High VAS, Good Effects VAS, Bad Effects VAS, and Any Effects VAS, are presented in Figures 2-6, respectively. These figures show that the mean response of all treatments peaked around 2 hours after treatment administration. The peak levels of Lorazepam 6 mg was the highest, the placebo the lowest, and the three doses of Ganaxolone (400 mg, 800 mg, and 2000 mg) in between with some overlaps after 6 hours for these measures. For Alertness/Drowsiness VAS (Figure 7), the trends of time courses were the opposite as seen in above Figures that the levels of Lorazepam 6 mg was the lowest, the placebo the highest, and the three doses of Ganaxolone (400 mg, 800 mg, and 2000 mg) in between those of Lorazepam 6 mg and placebo.

**Figure 2: Mean Time course of Drug Liking VAS (bipolar) (n=44).**

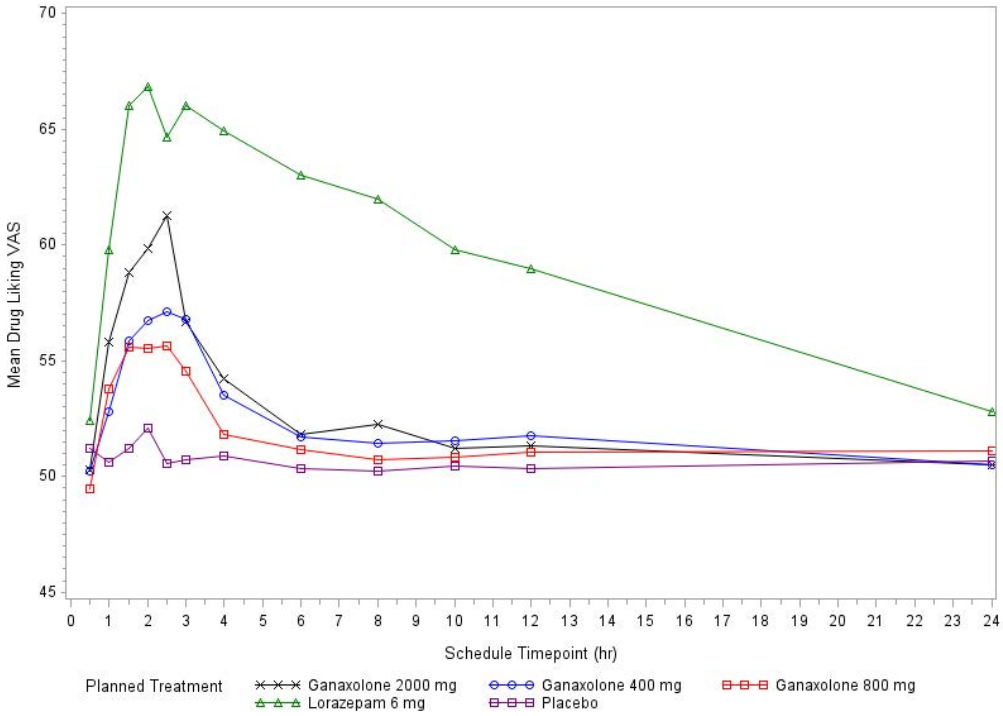



**Figure 3: Mean Time course of High VAS (unipolar) (n=44).**

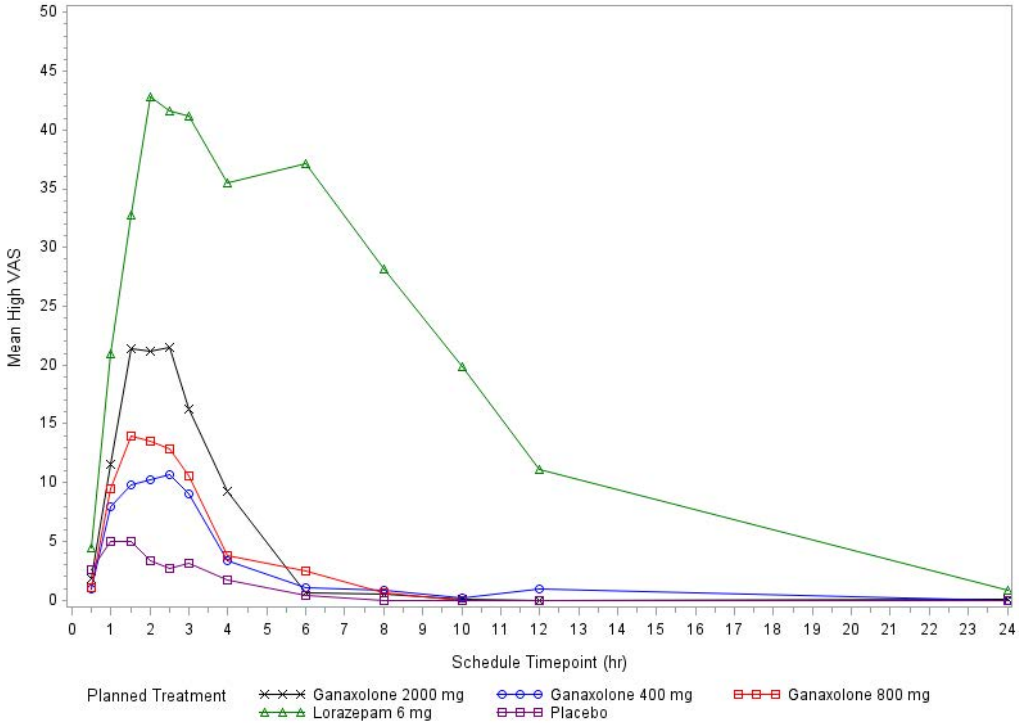


**Figure 4: Mean Time courses of Good Drug Effects VAS (unipolar) (n=44).**

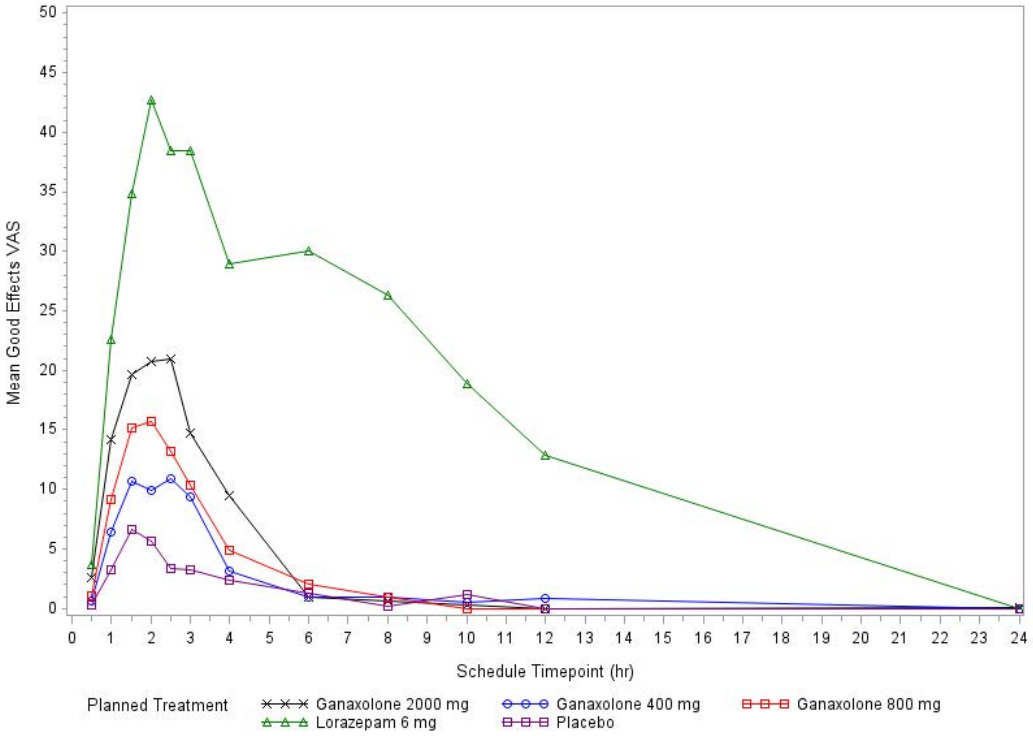



**Figure 5: Mean Time courses of Bad Drug Effects VAS (unipolar) (n=44).**

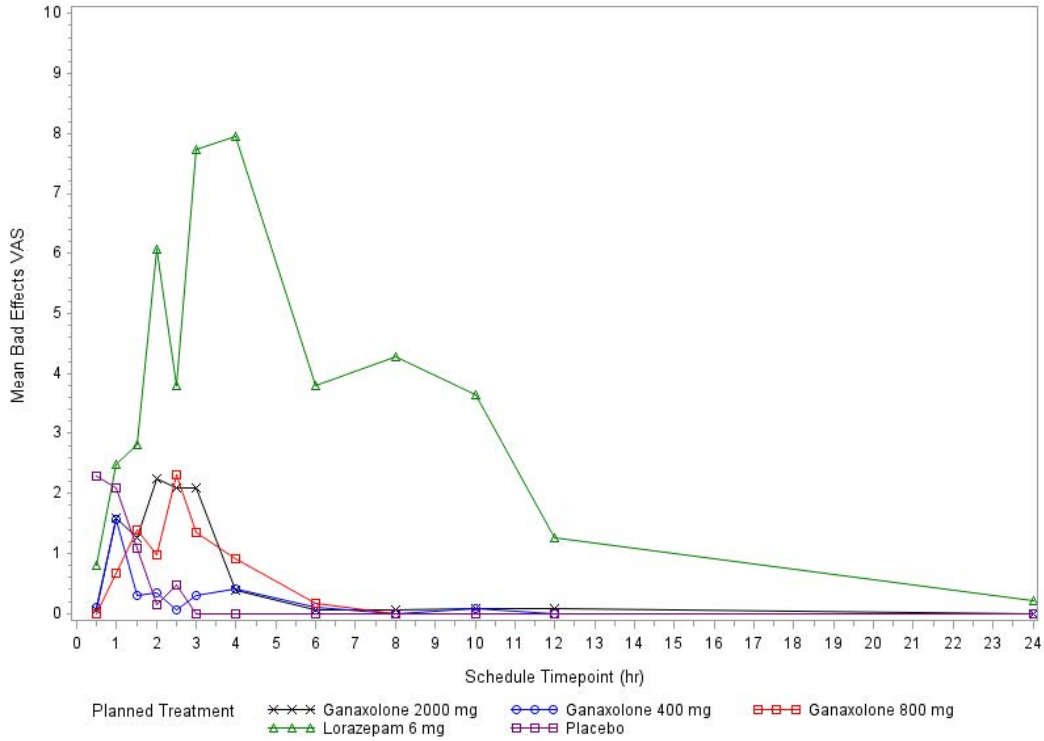


**Figure 6: Mean VAS Time courses of Any Effects (unipolar VAS) (n=44).**

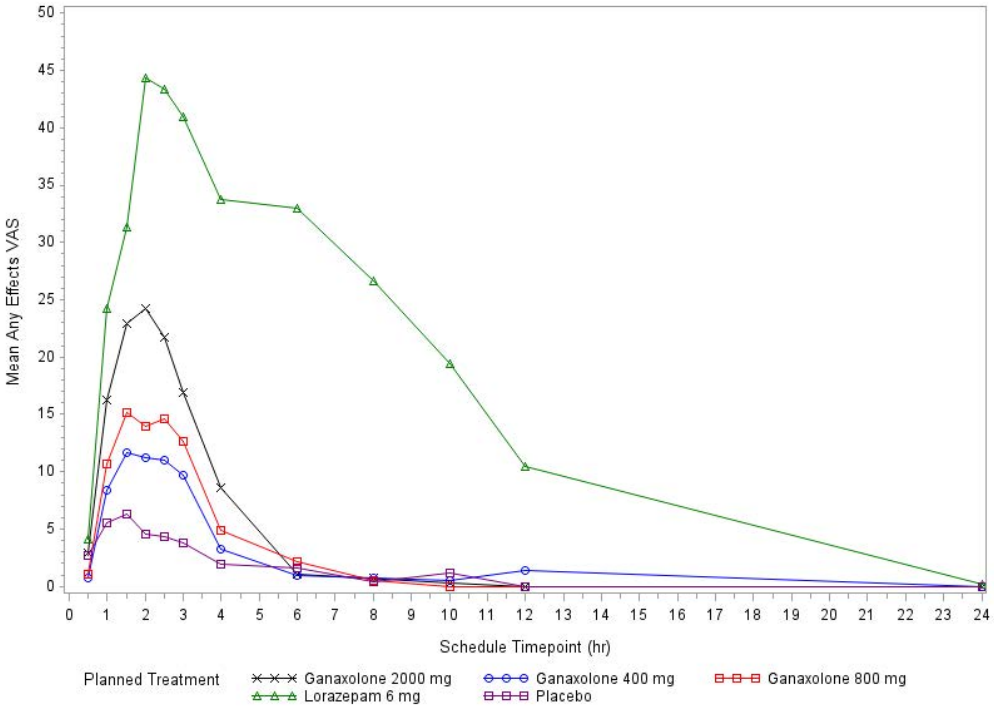
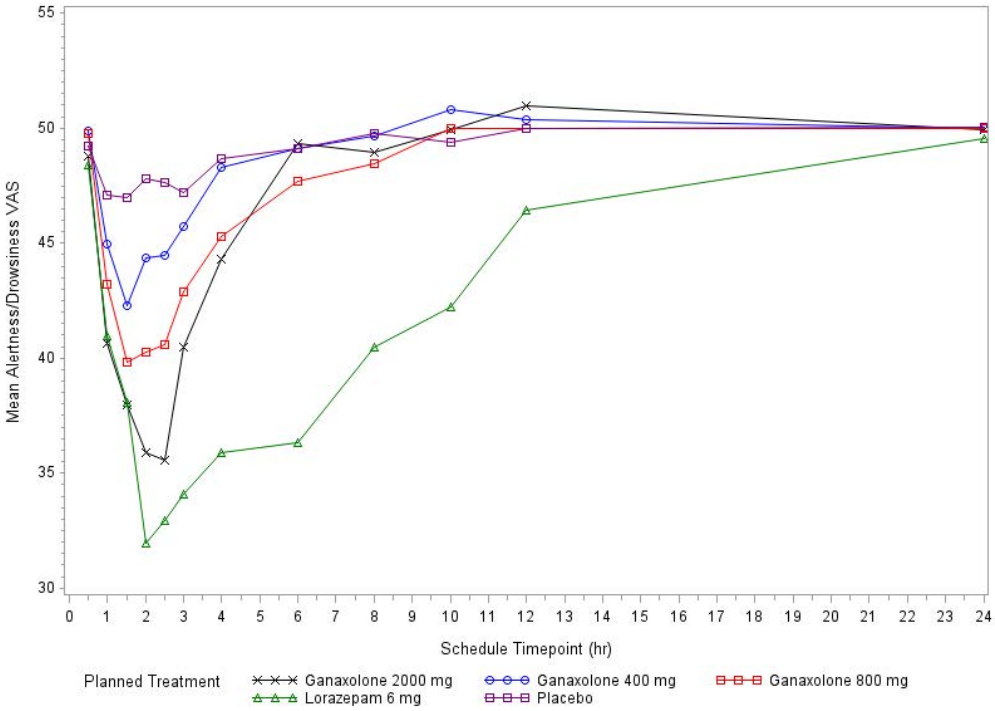



**Figure 7: Mean VAS Time courses of Alertness/Drowsiness (Bipolar VAS) (n=44).**



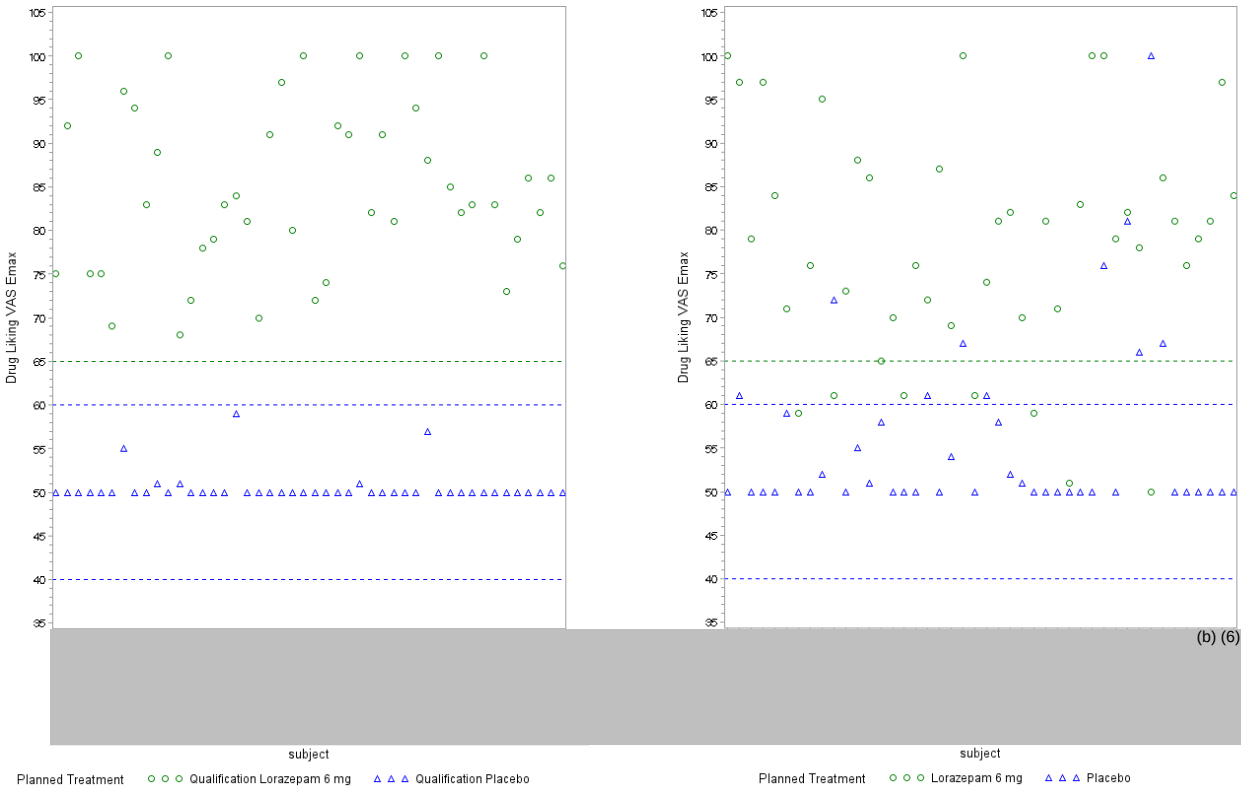
This reviewer identified that there were 3 subjects whose response to Lorazepam 6 mg were less than 60 points in Drug Liking VAS Emax, and 2 subjects whose response to placebo were larger than 65 in the Completer population as seen below in Table 2.

**Table 2. Problematic Subjects in Responding Treatments (Raw data, Completers)**

| SUBJID | param | TRTP | Emax | TRTP | Emax |
|---|---|---|---|---|---|
| (b) (6) | LIKEMAX | Lorazepam 6 mg | 50 | Placebo | 100 |
| | LIKEMAX | Lorazepam 6 mg | 59 | Placebo | 50 |
| | LIKEMAX | Lorazepam 6 mg | 51 | Placebo | 50 |
| | LIKEMAX | Lorazepam 6 mg | 61 | Placebo | 72 |

Figure 8 showed the subjects' responses in Drug Liking VAS Emax to the positive control (Lorazepam 6 mg) and placebo in the Qualification and Treatment phases, respectively. Based on the sponsor's qualification criteria, the Emax to the placebo should fall in the region 40-60 (the two bule lines) while the Emax to the positive control should be above 65 (the green line). The four problematic subjects listed in Table 2 can be identified in the plots for their abnormal responses. Two of the four problematic subjects were excluded from completer population for the Modified Completers population (MCP).

**Figure 8: Drug Liking VAS Emax to The Positive Control and Placebo Treatment in Qualification (N=46) and Treatment Phase (N=44)**



The descriptive statistics of the primary and some secondary endpoints on completer population are summarized in Table 3, containing the mean, standard deviation (SD), minimum (Min), the first quartile (Q1), median (Med), the third quartile (Q3), and maximum (Max) for the 5 treatments in the study. These results are consistent with those of the sponsor's analysis on completer population. The dose response trend of Ganaxolone was observed in the mean Drug Liking Emax and also in the Emaxs of High VAS, Good Drug Effects VSA, Bad Drug Effects VAS, and Any Drug Effects VAS, and the Emins of Alertness/Drowsiness VAS.

**Table 3. Descriptive Analysis of the Primary and Some Key Secondary Endpoints (Raw data, Completers, n=44)**

| Endpoint (Emax/Emin) | Treatment | N | Mean | SE | Min | Q1 | Median | Q3 | Max |
|---|---|---|---|---|---|---|---|---|---|
| Drug Liking VAS | Lorazepam 6 mg | 44 | 78.5 | 2.0 | 50 | 70.5 | 79 | 86.0 | 100 |
| Drug Liking VAS | Placebo | 44 | 55.7 | 1.6 | 50 | 50.0 | 50 | 58.5 | 100 |
| Drug Liking VAS | Ganaxolone 400 mg | 44 | 60.3 | 1.9 | 50 | 50.0 | 57 | 68.0 | 100 |
| Drug Liking VAS | Ganaxolone 800 mg | 44 | 61.5 | 1.8 | 50 | 50.0 | 57 | 73.0 | 87 |
| Drug Liking VAS | Ganaxolone 2000 mg | 44 | 65.5 | 2.1 | 46 | 52.0 | 64 | 76.0 | 100 |
| Overall Drug Liking VAS | Lorazepam 6 mg | 44 | 77.5 | 2.9 | 0 | 67.0 | 80 | 94.5 | 100 |
| Overall Drug Liking VAS | Placebo | 44 | 55.8 | 2.4 | 0 | 50.0 | 50 | 59.5 | 100 |
| Overall Drug Liking VAS | Ganaxolone 400 mg | 44 | 61.1 | 2.5 | 36 | 50.0 | 53 | 73.5 | 100 |
| Overall Drug Liking VAS | Ganaxolone 800 mg | 44 | 62.6 | 2.4 | 39 | 50.0 | 56 | 74.5 | 100 |
| Overall Drug Liking VAS | Ganaxolone 2000 mg | 44 | 67.3 | 3.2 | 0 | 50.0 | 66 | 84.5 | 100 |
| Take Drug Again VAS | Lorazepam 6 mg | 44 | 80.4 | 3.2 | 0 | 67.5 | 84 | 100.0 | 100 |
| Take Drug Again VAS | Placebo | 44 | 56.5 | 2.6 | 0 | 50.0 | 50 | 60.0 | 100 |
| Take Drug Again VAS | Ganaxolone 400 mg | 44 | 60.6 | 3.1 | 2 | 50.0 | 52 | 74.5 | 100 |
| Take Drug Again VAS | Ganaxolone 800 mg | 44 | 63.2 | 3.0 | 1 | 50.0 | 56 | 77.0 | 100 |
| Take Drug Again VAS | Ganaxolone 2000 mg | 44 | 67.9 | 3.7 | 0 | 50.0 | 66 | 87.0 | 100 |
| High VAS | Lorazepam 6 mg | 44 | 61.3 | 4.0 | 10 | 43.0 | 64 | 78.0 | 100 |
| High VAS | Placebo | 44 | 8.6 | 2.7 | 0 | 0.0 | 0 | 13.0 | 100 |
| High VAS | Ganaxolone 400 mg | 44 | 18.2 | 3.5 | 0 | 0.0 | 10 | 28.5 | 90 |
| High VAS | Ganaxolone 800 mg | 44 | 19.2 | 3.1 | 0 | 0.0 | 11 | 36.0 | 71 |
| High VAS | Ganaxolone 2000 mg | 44 | 29.8 | 4.0 | 0 | 7.5 | 20 | 47.0 | 92 |

**Table 3. Descriptive Analysis of the Primary and Some Key Secondary Endpoints (Raw data, Completers, n=44) (Continued.)**

| Endpoint (Emax/Emin) | Treatment | N | Mean | SE | Min | Q1 | Median | Q3 | Max |
|---|---|---|---|---|---|---|---|---|---|
| Good Effects VAS | Lorazepam 6 mg | 44 | 61.4 | 3.8 | 8 | 47 | 61.5 | 84 | 100 |
| Good Effects VAS | Placebo | 44 | 9.6 | 2.5 | 0 | 0 | 0 | 14 | 70 |
| Good Effects VAS | Ganaxolone 400 mg | 44 | 18.4 | 3.6 | 0 | 0 | 9.5 | 28 | 99 |
| Good Effects VAS | Ganaxolone 800 mg | 44 | 21.0 | 3.1 | 0 | 0 | 15 | 37 | 67 |
| Good Effects VAS | Ganaxolone 2000 mg | 44 | 30.0 | 3.9 | 0 | 9 | 24 | 54 | 94 |
| Bad Effects VAS | Lorazepam 6 mg | 44 | 19.3 | 4.0 | 0 | 0 | 7 | 41 | 100 |
| Bad Effects VAS | Placebo | 44 | 2.9 | 2.3 | 0 | 0 | 0 | 0 | 100 |
| Bad Effects VAS | Ganaxolone 400 mg | 44 | 2.2 | 1.5 | 0 | 0 | 0 | 0 | 66 |
| Bad Effects VAS | Ganaxolone 800 mg | 44 | 3.4 | 1.4 | 0 | 0 | 0 | 0 | 52 |
| Bad Effects VAS | Ganaxolone 2000 mg | 44 | 5.0 | 2.1 | 0 | 0 | 0 | 1 | 68 |
| Alertness/Drowsiness VAS | Lorazepam 6 mg | 44 | 21.8 | 2.0 | 0 | 13 | 22 | 32 | 48 |
| Alertness/Drowsiness VAS | Placebo | 44 | 43.4 | 1.5 | 13 | 41 | 48.5 | 50 | 50 |
| Alertness/Drowsiness VAS | Ganaxolone 400 mg | 44 | 37.0 | 2.0 | 2 | 28 | 39.5 | 50 | 50 |
| Alertness/Drowsiness VAS | Ganaxolone 800 mg | 44 | 35.1 | 1.8 | 17 | 24 | 37 | 47 | 50 |
| Alertness/Drowsiness VAS | Ganaxolone 2000 mg | 44 | 29.8 | 2.0 | 5 | 20 | 28 | 44 | 50 |
| Any Effects VAS | Lorazepam 6 mg | 44 | 62.9 | 3.8 | 14 | 46 | 61 | 81 | 100 |
| Any Effects VAS | Placebo | 44 | 11.9 | 3.1 | 0 | 0 | 0.5 | 16 | 98 |
| Any Effects VAS | Ganaxolone 400 mg | 44 | 20.4 | 3.7 | 0 | 0 | 13 | 31 | 100 |
| Any Effects VAS | Ganaxolone 800 mg | 44 | 21.3 | 3.2 | 0 | 0 | 16 | 35 | 65 |
| Any Effects VAS | Ganaxolone 2000 mg | 44 | 34.8 | 4.2 | 0 | 10 | 34.5 | 60 | 100 |
| Drug Liking VAS | Lorazepam 6 mg | 44 | 3.9 | 0.4 | 0.5 | 2 | 3 | 6 | 8 |
| Drug Liking VAS | Placebo | 44 | 1.3 | 0.2 | 0.5 | 1 | 0.5 | 2 | 8 |
| Drug Liking VAS | Ganaxolone 400 mg | 44 | 1.8 | 0.3 | 0.5 | 1 | 1.5 | 3 | 8 |
| Drug Liking VAS | Ganaxolone 800 mg | 44 | 1.6 | 0.2 | 0.5 | 1 | 1.5 | 2 | 6 |
| Drug Liking VAS | Ganaxolone 2000 mg | 44 | 2.1 | 0.2 | 0.5 | 1 | 2 | 3 | 8 |

3.7.2 Statistical Testing

To evaluate abuse potential of Ganaxolone, this reviewer carried out the following comparisons on the primary and key secondary endpoints:

- Validation: Lorazepam 6 mg - Placebo
- Lorazepam 6 mg - Ganaxolone 400 m
- Lorazepam 6 mg - Ganaxolone 800 m
- Lorazepam 6 mg - Ganaxolone 2000 m
- Ganaxolone 400 m – Placebo
- Ganaxolone 800 m - Placebo
- Ganaxolone 2000 m – Placebo

The statistical model used in the reviewer's primary analysis was a mixed-effects model which included sequence, period and treatment as fixed effects, and subject as a random effect. If the residuals from the mixed-effect model were normally distributed (e.g., *P* value ≥ 0.05), then it was to be determined whether the carryover effects should be included in the model (cutoff p-value=0.25).

Based on the sponsor's statistical analyses (Section 9.7 of the study report), the t-test was only used if the distribution of the paired difference was normal or slightly skewed, i.e., skewness=0 to 0.5 for upper-tailed test; skewness = −0.5 to 0 for lower-tailed test; and skewness= −0.5 to 0.5 for two-tailed test. Otherwise, median of the paired difference (Q1-Q3), 1-sided 95% or 2-sided 90% CI and *P* value from the sign test were output.

The Mixed-effects analysis showed that the first-order carryover effect was significant at 0.25 level (p-value=0.1204, see Appendix Table 1), so this factor was included in the Mixed-effects model of this reviewer. The normality assumption for conditional residuals in the mixed-effects model for the primary endpoint was examined (see Appendix Figure 1). The QQ-plot and residual distributions appear roughly normal. However, the W test on the residuals was significant (p=0.0026), not supporting the normality assumption. The null and alternative hypotheses for the normality analysis are shown below:

$H_0$: Distribution of residuals is normal
$H_a$: Distribution of residuals is not normal

Table 4 shows p-values of the W test and skewness of residuals for the primary and some secondary endpoints. The red p-value of the W-test showed the normality test was not significant at the level of 0.05. Based on the sponsor's criteria, the normality assumption was not rejected only for the secondary endpoints Overall Drug VAS Emax and Alertness/Drowsiness VAS Emin. Note that the skewness of the residuals for the primary endpoint is 0.4938 which is less than 0.5, the distribution of the residuals is roughly symmetric.

**Table 4: The W-Test results for the primary and some secondary endpoints (N=44)**

| Endpoint | skewness | W-statistics | p-value |
|---|---|---|---|
| Drug Liking VAS Emax | 0.4938 | 0.9793 | 0.0026 |
| Overall Drug Liking VAS Emax | -0.1879 | 0.9884 | 0.0712 |
| Take Drug Again VAS Emax | -0.6170 | 0.9738 | 0.0004 |
| High VAS Emax | 0.5616 | 0.9758 | 0.0008 |
| Good Effects VAS Emax | 0.5936 | 0.9735 | 0.0004 |
| Alertness/Drowsiness VAS Emin | -0.0244 | 0.9946 | 0.6286 |
| Any Effects VAS Emax | 0.4718 | 0.9839 | 0.0131 |
| Drug Liking VAS TEmax | 0.8613 | 0.9396 | 0.0000 |

Table 5 shows p-value of the W-test and skewness for each paired difference for Drug Liking Emax, Overall Drug Liking Emax, and Take Drug Again Emax; for other secondary endpoints see Appendix Table 2.

**Table 5: The W-Test results for the pairwise comparisons for Drug Liking Emax (N=44)**

| PARAM | Treatment difference | skewness | W-test p-value |
|---|---|---|---|
| Drug Liking VAS, Emax | Lorazepam 6 mg – Pcb | -1.6254 | 0.0004 |
| Drug Liking VAS, Emax | Lorazepam 6 mg - Ganaxolone 400 mg | -0.0725 | 0.7577 |
| Drug Liking VAS, Emax | Lorazepam 6 mg - Ganaxolone 800 mg | 0.2542 | 0.1822 |
| Drug Liking VAS, Emax | Lorazepam 6 mg - Ganaxolone 2000 mg | 0.8151 | 0.0347 |
| Drug Liking VAS, Emax | Ganaxolone 400 mg - Pcb | -0.2340 | 0.1020 |
| Drug Liking VAS, Emax | Ganaxolone 800 mg - Pcb | -0.9045 | 0.0019 |
| Drug Liking VAS, Emax | Ganaxolone 2000 mg - Pcb | -0.9475 | 0.0342 |
| Overall Drug Liking VSA, Emax | Lorazepam 6 mg – Pcb | 0.2117 | 0.0212 |
| Overall Drug Liking VSA, Emax | Lorazepam 6 mg - Ganaxolone 400 mg | -0.0372 | 0.3010 |
| Overall Drug Liking VSA, Emax | Lorazepam 6 mg - Ganaxolone 800 mg | -0.3721 | 0.0136 |
| Overall Drug Liking VSA, Emax | Lorazepam 6 mg - Ganaxolone 2000 mg | 0.4545 | 0.1728 |
| Overall Drug Liking VSA, Emax | Ganaxolone 400 mg - Pcb | -0.1603 | 0.1461 |
| Overall Drug Liking VSA, Emax | Ganaxolone 800 mg - Pcb | 0.1829 | 0.0001 |
| Overall Drug Liking VSA, Emax | Ganaxolone 2000 mg - Pcb | -0.3756 | 0.1212 |
| Take Drug Again VAS, Emax | Lorazepam 6 mg – Pcb | 0.1293 | 0.0005 |
| Take Drug Again VAS, Emax | Lorazepam 6 mg - Ganaxolone 400 mg | 0.6543 | 0.0220 |
| Take Drug Again VAS, Emax | Lorazepam 6 mg - Ganaxolone 800 mg | 0.0166 | 0.0045 |
| Take Drug Again VAS, Emax | Lorazepam 6 mg - Ganaxolone 2000 mg | 1.4672 | 0.0001 |
| Take Drug Again VAS, Emax | Ganaxolone 400 mg - Pcb | -0.3912 | 0.0114 |
| Take Drug Again VAS, Emax | Ganaxolone 800 mg - Pcb | -0.2869 | 0.0000 |
| Take Drug Again VAS, Emax | Ganaxolone 2000 mg - Pcb | -0.4793 | 0.0225 |

The primary analysis from the Mixed-effects model, paired t-test, and Sign test yield similar results. Table 6 summarized the primary analysis based on paired t-test, applying the Central Limit Theorem on the sample size of n=44. These results were basically consistent with those of the sponsor's analysis on completer population.

**Table 6. Summary of The Primary Analysis for Evaluating the Drug Abuse Potential of Ganaxolone (Completers, n=44).**

| | | | | | 95% CI* | | 95% CI** | |
|---|---|---|---|---|---|---|---|---|
| **Hypothesis Testing** | **margin** | **Mean** | **SE** | **p-value** | **LCL** | **UCL** | **LCL** | **UCL** |
| Lorazepam 6 mg – Pcb | 15 | 22.7 | 2.66 | 0.0029 | 18.3 | 27.2 | 17.4 | 28.1 |
| Lorazepam 6 mg - Ganaxolone 400 mg | 0 | 18.1 | 2.31 | 0.0000 | 14.3 | 22.0 | 13.5 | 22.8 |
| Lorazepam 6 mg - Ganaxolone 800 mg | 0 | 17.0 | 2.66 | 0.0000 | 12.5 | 21.4 | 11.6 | 22.3 |
| Lorazepam 6 mg - Ganaxolone 2000 mg | 0 | 13.0 | 2.16 | 0.0000 | 9.3 | 16.6 | 8.6 | 17.3 |
| Ganaxolone 400 mg - Pcb | 11 | 4.6 | 2.51 | 0.0072 | 0.4 | 8.8 | -0.5 | 9.7 |
| Ganaxolone 800 mg - Pcb | 11 | 5.8 | 2.33 | 0.0152 | 1.8 | 9.7 | 1.1 | 10.5 |
| Ganaxolone 2000 mg - Pcb | 11 | 9.8 | 2.71 | 0.3235 | 5.2 | 14.3 | 4.3 | 15.2 |

Note: Analyses were carried out in the Completers population using paired t-test
p-value was one-sided at alpha=0.05.
LCL: lower confidence limit, UCL: upper confidence limit. Pcb: Placebo.
* one-sided test; ** two-sided test.
Positice control vs. placebo (validation), $H_0$: $\mu_C - \mu_P \leq$ margin
Positive controls vs. Test drug (Relative Abuse Potential), $H_0$: $\mu_C - \mu_T \leq$ margine
Test drug vs. Placebo (Absolute Abuse Potential), $H_0$: $\mu_T - \mu_P \geq$ margin

Above results of the primary endpoint from the mixed model were summarized in Appendix Table 3.

The findings of the primary analyses on the completer population were summarized below:

1) the validation test for comparing the mean Drug Liking VAS Emax between Lorazepam 6 mg and placebo was statistically significant; the lower 95% confidence limit (one-sided) of the mean difference was greater than the test margin of 15 points.
2) for the relative abuse potential of Ganaxolone, the mean Emax of Drug Liking VAS to the treatment of Lorazepam 6 mg was statistically significantly greater than that of each Ganaxolone dose (400 mg, 800 mg, ang 2000 mg), suggesting that Ganaxolone at above doses was less liked than Lorazepam 6 mg at a level of 0.05 (one-sided) in healthy, male and female, non-dependent, recreational CNS depressant users.
3) for the absolute abuse potential of Ganaxolone, the null hypothesis of the mean Emax of Drug Liking VAS to Ganaxolone response being at least 11 points higher than that of placebo was rejected for the dose 400 mg and dose 800 mg, respectively, suggesting that drug liking of Ganaxolone at the two low doses was not significantly different from that of placebo. However, there was no sufficient evident to reject the null hypothesis for Ganaxolone 2000 mg – placebo because of the upper 95% confidence limit greater than 11, suggesting that Ganaxolone 2000 mg may have abuse potential.

The results of hypothesis tests on secondary endpoints are summarized in Table 7, supporting the results of the primary analysis.

**Table 7. Summary for Evaluating the Drug Abuse Potential of Ganaxolone on Overall Drug Liking VAS and Take Drug Again VAS (Completers, n=44).**

| | | | | | | 95% CI* | | 95% CI** | |
|---|---|---|---|---|---|---|---|---|---|
| **Endpoint** | **Pairwise Comparison** | **δ** | **Mean diff** | **SE** | **p-value** | **LCL** | **UCL** | **LCL** | **UCL** |
| Overall Drug Liking VAS Emax[a] | Lorazepam 6 mg - Pcb | 15 | 21.7 | 2.81 | 0.0101 | 17.0 | Inf | 16.1 | 27.4 |
| | Lorazepam 6 mg - Ganaxolone 400 mg | 0 | 16.6 | 2.84 | 0.0000 | 11.8 | Inf | 10.9 | 22.2 |
| | Lorazepam 6 mg -Ganaxolone 800 mg | 0 | 14.9 | 2.92 | 0.0000 | 10.0 | Inf | 9.0 | 20.7 |
| | Lorazepam 6 mg -Ganaxolone 2000 mg | 0 | 10.3 | 3.28 | 0.0013 | 4.8 | Inf | 3.7 | 16.9 |
| | Ganaxolone 400 mg - Pcb | 11 | 5.2 | 2.63 | 0.0156 | - Inf | 9.6 | -0.1 | 10.5 |
| | Ganaxolone 800 mg - Pcb | 11 | 6.9 | 2.72 | 0.0678 | - Inf | 11.4 | 1.4 | 12.3 |
| | Ganaxolone 2000 mg - Pcb | 11 | 11.4 | 3.10 | 0.5565 | - Inf | 16.6 | 5.2 | 17.6 |
| Take Drug Again VAS Emax[b] | Lorazepam 6 mg - Pcb | 15 | 23.9 | 2.81 | 0.0014 | 19.2 | Inf | 18.2 | 29.6 |
| | Lorazepam 6 mg -Ganaxolone 400 mg | 0 | 19.8 | 3.59 | 0.0000 | 13.8 | Inf | 12.6 | 27.1 |
| | Lorazepam 6 mg -Ganaxolone 800 mg | 0 | 17.2 | 3.28 | 0.0000 | 11.7 | Inf | 10.6 | 23.8 |
| | Lorazepam 6 mg - Ganaxolone 2000 mg | 0 | 12.5 | 3.53 | 0.0005 | 6.6 | Inf | 5.4 | 19.7 |
| | Ganaxolone 400 mg - Pcb | 11 | 4.1 | 3.31 | 0.0211 | -Inf | 9.6 | -2.6 | 10.7 |
| | Ganaxolone 800 mg - Pcb | 11 | 6.7 | 3.22 | 0.0948 | -Inf | 12.1 | 0.2 | 13.2 |
| | Ganaxolone 2000 mg - Pcb | 11 | 11.3 | 3.81 | 0.4645 | -Inf | 17.7 | 3.7 | 19.0 |
| High VAS Emax[b] | Lorazepam 6 mg - Pcb | 27 | 52.7 | 4.00 | 0.0000 | 46.0 | Inf | 44.7 | 60.8 |
| | Lorazepam 6 mg - Ganaxolone 400 mg | 0 | 43.1 | 4.53 | 0.0000 | 35.5 | Inf | 34.0 | 52.3 |
| | Lorazepam 6 mg -Ganaxolone 800 mg | 0 | 42.1 | 4.79 | 0.0000 | 34.1 | Inf | 32.5 | 51.8 |
| | Lorazepam 6 mg -Ganaxolone 2000 mg | 0 | 31.5 | 4.59 | 0.0000 | 23.8 | Inf | 22.2 | 40.7 |
| | Ganaxolone 400 mg - Pcb | 20 | 9.6 | 4.01 | 0.0064 | -Inf | 16.3 | 1.5 | 17.7 |
| | Ganaxolone 800 mg - Pcb | 20 | 10.6 | 3.85 | 0.0094 | -Inf | 17.1 | 2.8 | 18.4 |
| | Ganaxolone 2000 mg - Pcb | 20 | 21.3 | 4.76 | 0.3971 | -Inf | 29.3 | 11.7 | 30.8 |
| Good Effects VAS Emax[b] | Lorazepam 6 mg - Pcb[c] | 27 | 51.8 | 4.24 | 0.0000 | 44.6 | Inf | 43.2 | 60.3 |
| | Lorazepam 6 mg -Ganaxolone 400 mg | 0 | 43.0 | 4.64 | 0.0000 | 35.1 | Inf | 33.6 | 52.3 |
| | Lorazepam 6 mg -Ganaxolone 800 mg | 0 | 40.4 | 4.76 | 0.0000 | 32.4 | Inf | 30.8 | 50.0 |
| | Lorazepam 6 mg -Ganaxolone 2000 mg | 0 | 31.4 | 5.01 | 0.0000 | 22.9 | Inf | 21.3 | 41.5 |
| | Ganaxolone 400 mg - Pcb | 20 | 8.8 | 4.73 | 0.0113 | -Inf | 16.8 | -0.7 | 18.3 |
| | Ganaxolone 800 mg - Pcb | 20 | 11.4 | 3.07 | 0.0038 | -Inf | 16.6 | 5.2 | 17.6 |

| | | | | | | 95% CI* | | 95% CI** | |
|---|---|---|---|---|---|---|---|---|---|
| **Endpoint** | **Pairwise Comparison** | **δ** | **Mean diff** | **SE** | **p-value** | **LCL** | **UCL** | **LCL** | **UCL** |
| | Ganaxolone 2000 mg - Pcb | 20 | 20.4 | 4.52 | 0.4642 | -Inf | 28.0 | 11.3 | 29.5 |
| Bad Effects VAS Emax [b] | Lorazepam 6 mg - Pcb | 0 | 16.5 | 3.51 | 0.0000 | 10.6 | Inf | 9.4 | 23.5 |
| | Lorazepam 6 mg - Ganaxolone 400 mg | 0 | 17.2 | 3.53 | 0.0000 | 11.2 | Inf | 10.0 | 24.3 |
| | Lorazepam 6 mg -Ganaxolone 800 mg | 0 | 15.9 | 3.88 | 0.0001 | 9.4 | Inf | 8.1 | 23.8 |
| | Lorazepam 6 mg -Ganaxolone 2000 mg | 0 | 14.3 | 3.20 | 0.0000 | 8.9 | Inf | 7.9 | 20.8 |
| | Ganaxolone 400 mg - Pcb | 0 | -0.7 | 0.81 | 0.1948 | -Inf | 0.7 | -2.3 | 0.9 |
| | Ganaxolone 800 mg - Pcb | 0 | 0.5 | 2.63 | 0.4218 | -Inf | 4.9 | -4.8 | 5.8 |
| | Ganaxolone 2000 mg - Pcb | 0 | 2.1 | 1.76 | 0.1161 | -Inf | 5.1 | -1.4 | 5.7 |
| Alertness/ Drowsiness VAS Emin [a] | Lorazepam 6 mg - Pcb | 0 | -20.4 | 2.35 | 0.0000 | -Inf | -16.5 | -25.1 | -15.7 |
| | Lorazepam 6 mg -Ganaxolone 400 mg | 0 | -15.3 | 2.46 | 0.0000 | - Inf | -11.2 | -20.3 | -10.4 |
| | Lorazepam 6 mg -Ganaxolone 800 mg | 0 | -13.3 | 2.66 | 0.0000 | - Inf | -8.9 | -18.6 | -8.0 |
| | Lorazepam 6 mg - Ganaxolone 2000 mg | 0 | -7.9 | 2.57 | 0.0015 | - Inf | -3.6 | -13.1 | -2.8 |
| | Ganaxolone 400 mg - Pcb | 0 | -5.0 | 2.18 | 0.9881 | -8.7 | Inf | -9.4 | -0.7 |
| | Ganaxolone 800 mg - Pcb | 0 | -7.1 | 2.43 | 0.9976 | -11.1 | Inf | -11.9 | -2.2 |
| | Ganaxolone 2000 mg - Pcb | 0 | -12.5 | 2.32 | 1.0000 | -16.3 | Inf | -17.1 | -7.8 |
| Any Effects VAS Emax [b] | Lorazepam 6 mg - Pcb | 27 | 50.9 | 4.13 | 0.0000 | 44.0 | Inf | 42.6 | 59.3 |
| | Lorazepam 6 mg - Ganaxolone 400 mg | 0 | 42.5 | 4.61 | 0.0000 | 34.8 | Inf | 33.2 | 51.8 |
| | Lorazepam 6 mg -Ganaxolone 800 mg | 0 | 41.5 | 4.86 | 0.0000 | 33.4 | Inf | 31.7 | 51.3 |
| | Lorazepam 6 mg -Ganaxolone 2000 mg | 0 | 28.1 | 5.48 | 0.0000 | 18.9 | Inf | 17.1 | 39.2 |
| | Ganaxolone 400 mg - Pcb | 20 | 8.4 | 4.68 | 0.0087 | -Inf | 16.3 | -1.0 | 17.9 |
| | Ganaxolone 800 mg - Pcb | 20 | 9.4 | 4.02 | 0.0058 | -Inf | 16.2 | 1.3 | 17.5 |
| | Ganaxolone 2000 mg - Pcb | 20 | 22.8 | 5.04 | 0.2894 | -Inf | 31.3 | 12.7 | 33.0 |

Note: Analyses were carried out in the Completers population.

[a] Mixed-effects model; [b] paired t-test

p-value was one-sided at alpha=0.05.

LCL: lower confidence limit, UCL: upper confidence limit. Pcb: Placebo.

* one-sided test; ** two-sided test.

Positice control vs. placebo (validation), $H_0$: $\mu_C - \mu_P <= \boldsymbol{\delta}$

Positive controls vs. Test drug (Relative Abuse Potential), $H_0$: $\mu_C - \mu_T <= \boldsymbol{\delta}$

Test drug vs. Placebo (Absolute Abuse Potential), $H_0$: $\mu_T - \mu_P >= \boldsymbol{\delta}$

## Sensitivity Analysis

Currently we recommend all statistical analyses in a HAP study being conducted on a Modified

Completer Population (MCP). The recommended MCP is defined as completers who do not satisfy any of the following two criteria for the primary endpoint Drug Liking Emax:

1. The difference between maximum and minimum of Emax scores for all treatments is smaller than or equal to 5 (that is, similar Emax scores across all treatments including placebo).
2. Emax (P) > 60 and Emax(P) – Emax(Z30) >=5 (or Emax(P) – Emax(S150) >=5)

After applying two criteria above, two subjects were excluded ([redacted] (b) (6)), the MCP population includes 42 subjects.

The analysis results of MCP population for the primary outcome of Drug Liking Emax are:

**Table 8: Sensitivity Analysis Results on Drug Liking $E_{max}$ for MCP Population (N= 42)**

| Pairwise Comparison | Mean Diff /Med Diff | StdErr /IQR | Test Margin | p-value | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | LCL | UCL |
| Lorazepam 6 mg - Pcb | 25.3 | 1.9 | 15 | <.0001 | 22.1 | Inf |
| Lorazepam 6 mg - Ganaxolone 400 mg | 19.7 | 2.5 | 0 | <.0001 | 15.7 | Inf |
| Lorazepam 6 mg - Ganaxolone 800 mg | 18.0 | 2.4 | 0 | <.0001 | 14.0 | Inf |
| Lorazepam 6 mg - Ganaxolone 2000 mg | 13.4 | 2.4 | 0 | <.0001 | 9.2 | Inf |
| Ganaxolone 400 mg - Pcb | 5.6 | 2.0 | 11 | 0.005 | -Inf | 8.9 |
| Ganaxolone 800 mg - Pcb | 7.2 | 2.1 | 11 | 0.04 | -Inf | 10.7 |
| Ganaxolone 2000 mg - Pcb | 11.8 | 2.2 | 11 | 0.65 | -Inf | 15.5 |

The results indicated that the analysis of Drug Liking Emax were consistent with the results from the completers population.

The analysis results for the two key secondary outcomes of Emax Overall Drug Liking VAS and Take Drug Again VAS were also consistent with the results from completers population.

### Drug Similarity Analysis

The Drug Similarity VAS assesses how similar the effects were as compared to other recreational drugs previously consumed by the study subject. The following question was asked:

- How similar is the drug you most recently received to [drug name]?

It is a unipolar scale ranging from 0 (i.e., not at all similar) to 100 points (i.e., very similar). The data for Drug Similarity VAS were collected at hour 12 post-dose.

Table 9 shows the descriptive statistics for subjects' responses to the comparisons between each treatment and each drug. The N denotes the number of subjects who gave a response for such a comparison. Based on Drug Similarity VAS data, the perceived effects of Benzodiazepines were more similar to the effects of Lorazepam 6 mg (68.2), and placebo is more similar to placebo (54.8). For the test drug, Benzodiazepines were more similar to Ganaxolone, and the next Opioids.

**Table 9: Summary Statistics for Drug Similarity VAS at hour 12**

| Drug | Treatment | N | Mean | SE | L95CI | U95CI | Min | Q1 | Median | Q3 | Max |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Benzodiazepines | Ganaxolone 2000 mg | 44 | 48.6 | 6.2 | 36.1 | 61.1 | 0 | 4.5 | 43 | 100.0 | 100 |
| Benzodiazepines | Ganaxolone 400 mg | 44 | 28.0 | 5.4 | 17.2 | 38.8 | 0 | 0.0 | 8 | 58.0 | 100 |
| Benzodiazepines | Ganaxolone 800 mg | 44 | 30.4 | 5.1 | 20.1 | 40.6 | 0 | 0.0 | 24 | 48.5 | 100 |
| Benzodiazepines | Lorazepam 6 mg | 44 | 68.2 | 5.2 | 57.8 | 78.6 | 0 | 45.0 | 80 | 99.0 | 100 |
| Benzodiazepines | Placebo | 44 | 17.5 | 5.0 | 7.3 | 27.6 | 0 | 0.0 | 0 | 14.5 | 100 |
| Placebo | Ganaxolone 2000 mg | 44 | 24.1 | 6.3 | 11.5 | 36.8 | 0 | 0.0 | 0 | 41.0 | 100 |
| Placebo | Ganaxolone 400 mg | 44 | 35.9 | 7.2 | 21.3 | 50.5 | 0 | 0.0 | 0 | 100.0 | 100 |
| Placebo | Ganaxolone 800 mg | 44 | 30.7 | 6.7 | 17.3 | 44.1 | 0 | 0.0 | 0 | 89.5 | 100 |
| Placebo | Lorazepam 6 mg | 44 | 2.7 | 2.3 | -1.9 | 7.3 | 0 | 0.0 | 0 | 0.0 | 100 |
| Placebo | Placebo | 44 | 54.8 | 7.2 | 40.2 | 69.3 | 0 | 0.0 | 83 | 100.0 | 100 |
| THC | Ganaxolone 2000 mg | 44 | 11.1 | 3.1 | 4.9 | 17.4 | 0 | 0.0 | 1 | 13.5 | 87 |
| THC | Ganaxolone 400 mg | 44 | 9.8 | 3.5 | 2.8 | 16.8 | 0 | 0.0 | 0 | 4.0 | 100 |
| THC | Ganaxolone 800 mg | 44 | 10.9 | 3.3 | 4.2 | 17.7 | 0 | 0.0 | 0 | 12.0 | 96 |
| THC | Lorazepam 6 mg | 44 | 25.8 | 4.7 | 16.3 | 35.3 | 0 | 0.0 | 12 | 47.0 | 100 |
| THC | Placebo | 44 | 9.3 | 3.8 | 1.7 | 16.8 | 0 | 0.0 | 0 | 0.5 | 100 |
| Opioids | Ganaxolone 2000 mg | 36 | 21.8 | 4.9 | 11.8 | 31.8 | 0 | 0.0 | 6 | 43.0 | 100 |
| Opioids | Ganaxolone 400 mg | 36 | 16.3 | 4.9 | 6.4 | 26.2 | 0 | 0.0 | 0 | 18.5 | 100 |
| Opioids | Ganaxolone 800 mg | 36 | 16.1 | 4.5 | 6.9 | 25.3 | 0 | 0.0 | 0 | 18.5 | 100 |
| Opioids | Lorazepam 6 mg | 36 | 32.3 | 5.8 | 20.5 | 44.2 | 0 | 0.0 | 24 | 52.0 | 100 |
| Opioids | Placebo | 36 | 10.8 | 4.9 | 0.9 | 20.6 | 0 | 0.0 | 0 | 0.0 | 100 |
| Ethanol | Ganaxolone 2000 mg | 31 | 2.6 | 1.2 | 0.2 | 5.1 | 0 | 0.0 | 0 | 0.0 | 32 |
| Ethanol | Ganaxolone 400 mg | 31 | 4.4 | 3.3 | -2.3 | 11.1 | 0 | 0.0 | 0 | 0.0 | 100 |
| Ethanol | Ganaxolone 800 mg | 31 | 4.6 | 3.2 | -1.9 | 11.1 | 0 | 0.0 | 0 | 0.0 | 96 |
| Ethanol | Lorazepam 6 mg | 31 | 10.8 | 4.1 | 2.3 | 19.2 | 0 | 0.0 | 0 | 13.0 | 99 |
| Ethanol | Placebo | 31 | 3.8 | 3.3 | -2.9 | 10.4 | 0 | 0.0 | 0 | 0.0 | 100 |

**Table 9: Summary Statistics for Drug Similarity VAS at hour 12 (n<30) (continued-1)**

| Endpoint | Treatment | N | Mean | SE | L95CI | U95CI | Min | Q1 | Median | Q3 | Max |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cocaine | Ganaxolone 2000 mg | 27 | 0.0 | 0.0 | . | . | 0 | 0.0 | 0 | 0.0 | 0 |
| Cocaine | Ganaxolone 400 mg | 27 | 0.0 | 0.0 | . | . | 0 | 0.0 | 0 | 0.0 | 0 |
| Cocaine | Ganaxolone 800 mg | 27 | 0.0 | 0.0 | . | . | 0 | 0.0 | 0 | 0.0 | 0 |
| Cocaine | Lorazepam 6 mg | 27 | 0.3 | 0.2 | -0.2 | 0.7 | 0 | 0.0 | 0 | 0.0 | 6 |
| Cocaine | Placebo | 27 | 0.0 | 0.0 | . | . | 0 | 0.0 | 0 | 0.0 | 0 |
| Ecstasy (MDMA) | Ganaxolone 2000 mg | 19 | 0.1 | 0.1 | -0.1 | 0.2 | 0 | 0.0 | 0 | 0.0 | 1 |
| Ecstasy (MDMA) | Ganaxolone 400 mg | 19 | 0.0 | 0.0 | . | . | 0 | 0.0 | 0 | 0.0 | 0 |
| Ecstasy (MDMA) | Ganaxolone 800 mg | 19 | 0.1 | 0.1 | -0.1 | 0.2 | 0 | 0.0 | 0 | 0.0 | 1 |
| Ecstasy (MDMA) | Lorazepam 6 mg | 19 | 0.6 | 0.4 | -0.3 | 1.4 | 0 | 0.0 | 0 | 0.0 | 6 |
| Ecstasy (MDMA) | Placebo | 19 | 0.1 | 0.1 | -0.1 | 0.2 | 0 | 0.0 | 0 | 0.0 | 1 |
| d-amphetamine | Ganaxolone 2000 mg | 15 | 0.0 | 0.0 | . | . | 0 | 0.0 | 0 | 0.0 | 0 |
| d-amphetamine | Ganaxolone 400 mg | 15 | 0.0 | 0.0 | . | . | 0 | 0.0 | 0 | 0.0 | 0 |
| d-amphetamine | Ganaxolone 800 mg | 15 | 0.0 | 0.0 | . | . | 0 | 0.0 | 0 | 0.0 | 0 |
| d-amphetamine | Lorazepam 6 mg | 15 | 0.6 | 0.6 | -0.7 | 1.9 | 0 | 0.0 | 0 | 0.0 | 9 |
| d-amphetamine | Placebo | 15 | 0.0 | 0.0 | . | . | 0 | 0.0 | 0 | 0.0 | 0 |
| Codeine | Ganaxolone 2000 mg | 6 | 37.3 | 17.8 | -8.4 | 83.0 | 0 | 0.0 | 21 | 82.0 | 100 |
| Codeine | Ganaxolone 400 mg | 6 | 18.2 | 13.4 | -16.2 | 52.5 | 0 | 0.0 | 0 | 28.0 | 81 |
| Codeine | Ganaxolone 800 mg | 6 | 11.0 | 5.4 | -3.0 | 25.0 | 0 | 0.0 | 8 | 19.0 | 32 |
| Codeine | Lorazepam 6 mg | 6 | 22.2 | 10.6 | -5.2 | 49.5 | 0 | 0.0 | 15 | 45.0 | 59 |
| Codeine | Placebo | 6 | 15.7 | 9.8 | -9.6 | 40.9 | 0 | 0.0 | 7 | 18.0 | 62 |
| Sedatives | Ganaxolone 2000 mg | 2 | 48.5 | 0.0 | -567.8 | 664.8 | 0 | 0.0 | 49 | 97.0 | 97 |
| Sedatives | Ganaxolone 400 mg | 2 | 0.0 | 0.0 | . | . | 0 | 0.0 | 0 | 0.0 | 0 |
| Sedatives | Ganaxolone 800 mg | 2 | 9.0 | 0.0 | -105.4 | 123.4 | 0 | 0.0 | 9 | 18.0 | 18 |
| Sedatives | Lorazepam 6 mg | 2 | 95.0 | 0.0 | 56.9 | 133.1 | 92 | 92.0 | 95 | 98.0 | 98 |
| Sedatives | Placebo | 2 | 28.5 | 0.0 | -333.6 | 390.6 | 0 | 0.0 | 29 | 57.0 | 57 |

**Table 9: Summary Statistics for Drug Similarity VAS at hour 12 (n<30) (continued-2)**

| Endpoint | Treatment | N | Mean | SE | L95CI | U95CI | Min | Q1 | Median | Q3 | Max |
|---|---|---|---|---|---|---|---|---|---|---|---|
| LSD | Ganaxolone 2000 mg | 1 | 0.0 | | | | 0 | 0 | 0 | 0 | 0 |
| LSD | Ganaxolone 400 mg | 1 | 0.0 | | | | 0 | 0 | 0 | 0 | 0 |
| LSD | Ganaxolone 800 mg | 1 | 0.0 | | | | 0 | 0 | 0 | 0 | 0 |
| LSD | Lorazepam 6 mg | 1 | 0.0 | | | | 0 | 0 | 0 | 0 | 0 |
| LSD | Placebo | 1 | 0.0 | | | | 0 | 0 | 0 | 0 | 0 |
| Phencyclidine (PCP) | Ganaxolone 2000 mg | 1 | 0.0 | | | | 0 | 0 | 0 | 0 | 0 |
| Phencyclidine (PCP) | Ganaxolone 400 mg | 1 | 0.0 | | | | 0 | 0 | 0 | 0 | 0 |
| Phencyclidine (PCP) | Ganaxolone 800 mg | 1 | 0.0 | | | | 0 | 0 | 0 | 0 | 0 |
| Phencyclidine (PCP) | Lorazepam 6 mg | 1 | 0.0 | | | | 0 | 0 | 0 | 0 | 0 |
| Phencyclidine (PCP) | Placebo | 1 | 0.0 | | | | 0 | 0 | 0 | 0 | 0 |
| Barbiturates | Ganaxolone 2000 mg | 0 | | | | | | | | | |
| Barbiturates | Ganaxolone 400 mg | 0 | | | | | | | | | |
| Barbiturates | Ganaxolone 800 mg | 0 | | | | | | | | | |
| Barbiturates | Lorazepam 6 mg | 0 | | | | | | | | | |
| Barbiturates | Placebo | 0 | | | | | | | | | |
| Heroin | Ganaxolone 2000 mg | 0 | | | | | | | | | |
| Heroin | Ganaxolone 400 mg | 0 | | | | | | | | | |
| Heroin | Ganaxolone 800 mg | 0 | | | | | | | | | |
| Heroin | Lorazepam 6 mg | 0 | | | | | | | | | |
| Heroin | Placebo | 0 | | | | | | | | | |
| Ketamine (Special K) | Ganaxolone 2000 mg | 0 | | | | | | | | | |
| Ketamine (Special K) | Ganaxolone 400 mg | 0 | | | | | | | | | |
| Ketamine (Special K) | Ganaxolone 800 mg | 0 | | | | | | | | | |
| Ketamine (Special K) | Lorazepam 6 mg | 0 | | | | | | | | | |
| Ketamine (Special K) | Placebo | 0 | | | | | | | | | |
| Pseudophedrine | Ganaxolone 2000 mg | 0 | | | | | | | | | |
| Pseudophedrine | Ganaxolone 400 mg | 0 | | | | | | | | | |
| Pseudophedrine | Ganaxolone 800 mg | 0 | | | | | | | | | |
| Pseudophedrine | Lorazepam 6 mg | 0 | | | | | | | | | |
| Pseudophedrine | Placebo | 0 | | | | | | | | | |

# 4. SUMMARY AND CONCLUSIONS

## 4.1 Statistical Issues

NA.

## 4.2 Conclusions and Recommendations

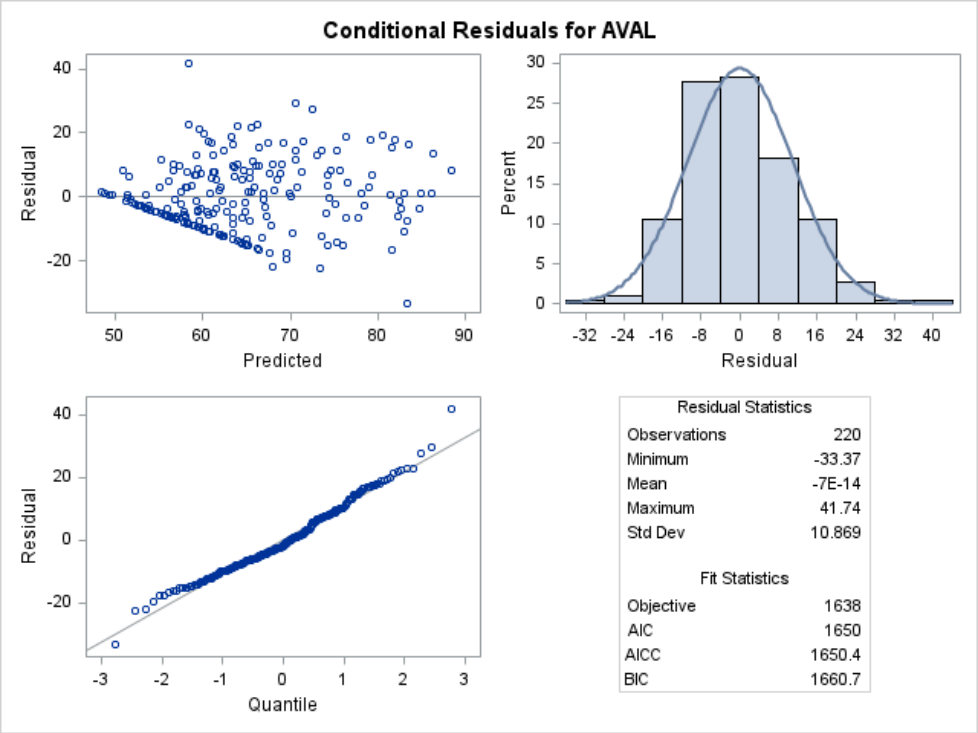
The reviewer's primary analysis was conducted on Completers population. This reviewer confirmed the following findings:

1. the validation test for comparing the mean Drug Liking VAS Emax between Lorazepam 6 mg and placebo was statistically significant; the lower 95% confidence limit (one-sided) of the mean difference was 18.8 points, greater than the test margin of 15 points.
2. for the relative abuse potential of Ganaxolone, the mean Emax of Drug Liking VAS to the treatment of Lorazepam 6 mg was statistically significantly greater than that of each Ganaxolone dose (400 mg, 800 mg, ang 2000 mg), suggesting that Ganaxolone at above doses was less liked than Lorazepam 6 mg at a level of 0.05 (one-sided) in healthy, male and female, non-dependent, recreational CNS depressant users.
3. for the absolute abuse potential of Ganaxolone, the null hypothesis of the mean Emax of Drug Liking VAS to Ganaxolone response being at least 11 points higher than that of placebo was rejected for the dose 400 mg and dose 800 mg, respectively, suggesting that drug liking of Ganaxolone at the two low doses was not significantly different from that of placebo. However, there was no sufficient evident to reject the null hypothesis for Ganaxolone 2000 mg – placebo because of the upper 95% confidence limit greater than 11, suggesting that Ganaxolone 2000 mg may have abuse potential.

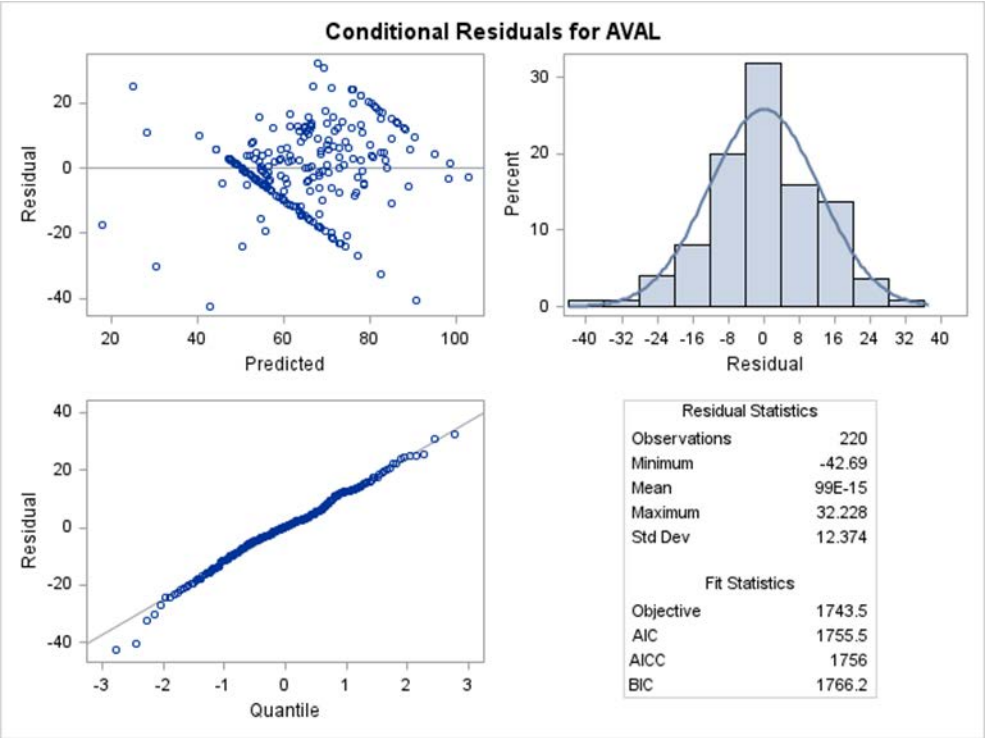
The results of the primary analysis were supported by the analysis of key secondary endpoints. Additional supportive results come from the consistent positive dose response in the mean Emax of the primary and key secondary endpoints.

## Appendix

Figure 1: Normal plots of the conditional residuals in the Mixed-effects model analysis for Drug Liking VAS Emax.
A. Drug Liking VAS Emax.




B. Overall Drug Liking VAS Emax



C. Alertness/Drowsiness VAS Emin

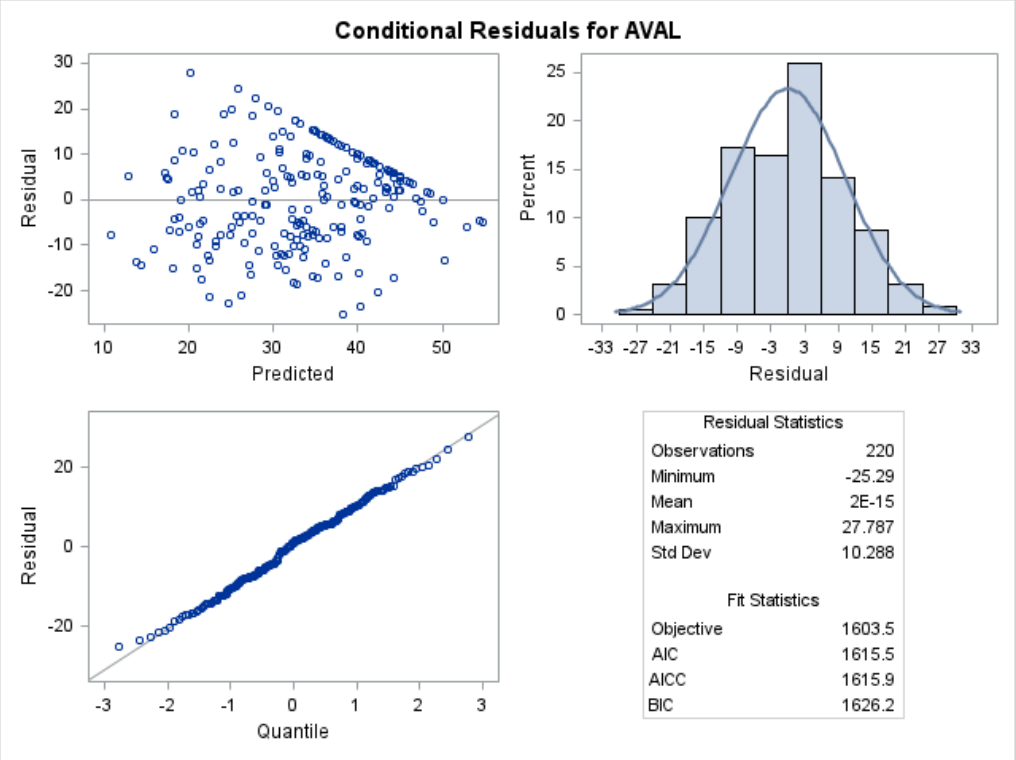



Table 1: Test of the fixed effects in Mixed-effects model for the Primary endpoint

| Type 3 Tests of Fixed Effects | | | | |
|---|---|---|---|---|
| **Effect** | **Num DF** | **Den DF** | **F Value** | **Pr > F** |
| **trt** | 4 | 164 | 21.80 | <.0001 |
| **sequence** | 9 | 34 | 1.08 | 0.4044 |
| **period** | 4 | 164 | 4.01 | 0.0040 |
| **carry** | 4 | 164 | 1.86 | 0.1204 |

For Overall Drug Liking VAS Emax

| Type 3 Tests of Fixed Effects | | | | |
|---|---|---|---|---|
| **Effect** | **Num DF** | **Den DF** | **F Value** | **Pr > F** |
| **trt** | 4 | 164 | 14.38 | <.0001 |
| **sequence** | 9 | 34 | 0.28 | 0.9746 |
| **period** | 4 | 164 | 1.68 | 0.1573 |
| **carry** | 4 | 164 | 2.16 | 0.0755 |

For Alertness/Drowsiness VAS Emin

| Type 3 Tests of Fixed Effects | | | | |
|---|---|---|---|---|
| **Effect** | **Num DF** | **Den DF** | **F Value** | **Pr > F** |
| **trt** | 4 | 164 | 21.23 | <.0001 |
| **sequence** | 9 | 34 | 1.65 | 0.1410 |
| **period** | 4 | 164 | 3.61 | 0.0076 |
| **carry** | 4 | 164 | 2.04 | 0.0912 |

Table 2: The W-Test results for the pairwise comparisons for Secondary Endpoints (n=44)

| PARAM | Treatment difference | skewness | pnorm |
|---|---|---|---|
| High VAS, Emax | Lorazepam 6 mg – Pcb | 0.1839 | 0.3223 |
| High VAS, Emax | Lorazepam 6 mg - Ganaxolone 400 mg | -0.0731 | 0.3537 |
| High VAS, Emax | Lorazepam 6 mg - Ganaxolone 800 mg | 0.3971 | 0.0108 |
| High VAS, Emax | Lorazepam 6 mg - Ganaxolone 2000 mg | 0.3971 | 0.0108 |
| High VAS, Emax | Ganaxolone 400 mg - Pcb | 0.5113 | 0.0256 |
| High VAS, Emax | Ganaxolone 800 mg - Pcb | -1.5745 | 0.0000 |
| High VAS, Emax | Ganaxolone 2000 mg - Pcb | -0.0583 | 0.8761 |
| Good Effects VA, Emax | Lorazepam 6 mg – Pcb | -0.0231 | 0.2727 |
| Good Effects VA, Emax | Lorazepam 6 mg - Ganaxolone 400 mg | 0.0043 | 0.1264 |
| Good Effects VA, Emax | Lorazepam 6 mg - Ganaxolone 800 mg | 0.5513 | 0.0116 |
| Good Effects VA, Emax | Lorazepam 6 mg - Ganaxolone 2000 mg | 0.5513 | 0.0116 |
| Good Effects VA, Emax | Ganaxolone 400 mg - Pcb | 0.0619 | 0.3438 |
| Good Effects VA, Emax | Ganaxolone 800 mg - Pcb | 0.6233 | 0.0203 |
| Good Effects VA, Emax | Ganaxolone 2000 mg - Pcb | 0.1691 | 0.8766 |
| Bad Effects VAS, Emax | Lorazepam 6 mg – Pcb | 1.3104 | 0.0000 |
| Bad Effects VAS, Emax | Lorazepam 6 mg - Ganaxolone 400 mg | 1.2141 | 0.0000 |
| Bad Effects VAS, Emax | Lorazepam 6 mg - Ganaxolone 800 mg | 1.5311 | 0.0000 |
| Bad Effects VAS, Emax | Lorazepam 6 mg - Ganaxolone 2000 mg | 1.5311 | 0.0000 |
| Bad Effects VAS, Emax | Ganaxolone 400 mg - Pcb | -5.7736 | 0.0000 |
| Bad Effects VAS, Emax | Ganaxolone 800 mg - Pcb | -4.1654 | 0.0000 |
| Bad Effects VAS, Emax | Ganaxolone 2000 mg - Pcb | 2.2389 | 0.0000 |
| Alertness/Drowsiness VAS, Emin | Lorazepam 6 mg – Pcb | 0.0755 | 0.6603 |
| Alertness/Drowsiness VAS, Emin | Lorazepam 6 mg - Ganaxolone 400 mg | 0.4162 | 0.4495 |
| Alertness/Drowsiness VAS, Emin | Lorazepam 6 mg - Ganaxolone 800 mg | -0.1415 | 0.5467 |
| Alertness/Drowsiness VAS, Emin | Lorazepam 6 mg - Ganaxolone 2000 mg | -0.1415 | 0.5467 |
| Alertness/Drowsiness VAS, Emin | Ganaxolone 400 mg - Pcb | 0.3258 | 0.3891 |
| Alertness/Drowsiness VAS, Emin | Ganaxolone 800 mg - Pcb | 0.5112 | 0.0243 |
| Alertness/Drowsiness VAS, Emin | Ganaxolone 2000 mg - Pcb | 0.7002 | 0.2289 |
| Any Effects VAS, Emax | Lorazepam 6 mg – Pcb | -0.0873 | 0.5768 |
| Any Effects VAS, Emax | Lorazepam 6 mg - Ganaxolone 400 mg | 0.0292 | 0.3487 |
| Any Effects VAS, Emax | Lorazepam 6 mg - Ganaxolone 800 mg | 0.1872 | 0.1513 |
| Any Effects VAS, Emax | Lorazepam 6 mg - Ganaxolone 2000 mg | 0.1872 | 0.1513 |
| Any Effects VAS, Emax | Ganaxolone 400 mg - Pcb | 0.0695 | 0.7298 |
| Any Effects VAS, Emax | Ganaxolone 800 mg - Pcb | -1.1870 | 0.0004 |
| Any Effects VAS, Emax | Ganaxolone 2000 mg - Pcb | -0.0050 | 0.8913 |
| Drug Liking VAS, TEmax | Lorazepam 6 mg – Pcb | 0.1763 | 0.0226 |
| Drug Liking VAS, TEmax | Lorazepam 6 mg - Ganaxolone 400 mg | -1.0577 | 0.0023 |
| Drug Liking VAS, TEmax | Lorazepam 6 mg - Ganaxolone 800 mg | 0.1885 | 0.0939 |
| Drug Liking VAS, TEmax | Lorazepam 6 mg - Ganaxolone 2000 mg | 0.1885 | 0.0939 |
| Drug Liking VAS, TEmax | Ganaxolone 400 mg - Pcb | 0.4574 | 0.0106 |
| Drug Liking VAS, TEmax | Ganaxolone 800 mg - Pcb | -0.4612 | 0.0010 |
| Drug Liking VAS, TEmax | Ganaxolone 2000 mg - Pcb | -0.6339 | 0.0001 |

**Table 3. Summary of The Primary Analysis for Evaluating the Drug Abuse Potential of Ganaxolone (Completers, n=44).**

**LS-Mean Emax for Primary Endpoint of Drug Liking VAS Emax (N=44)**

| Endpoint | Treatment | LSmean | StdErr |
|---|---|---|---|
| Drug Liking VAS Emax | Lorazepam 6 mg | 78.4 | 2.0 |
| Drug Liking VAS Emax | Placebo | 55.6 | 1.7 |
| Drug Liking VAS Emax | Ganaxolone 400 mg | 60.1 | 1.8 |
| Drug Liking VAS Emax | Ganaxolone 800 mg | 61.3 | 1.9 |
| Drug Liking VAS Emax | Ganaxolone 2000 mg | 65.2 | 2.0 |
| Note: Analyses were carried out in the Completers population. | | | |

| | | | | | 95% CI* | | 95% CI** | |
|---|---|---|---|---|---|---|---|---|
| **Hypothesis Testing** | **margin** | **Mean diff** | **SE** | **p-value** | **LCL** | **UCL** | **LCL** | **UCL** |
| Lorazepam 6 mg – Pcb | 15 | 22.8<br>26 | 2.4 | 0.0009 | 18.8 | Inf | 18.0 | 27.7 |
| Lorazepam 6 mg - Ganaxolone 400 mg | 0 | 18.3 | 2.5 | 0.0000 | 14.1 | Inf | 13.3 | 23.4 |
| Lorazepam 6 mg - Ganaxolone 800 mg | 0 | 17.1 | 2.6 | 0.0000 | 12.8 | Inf | 12.0 | 22.3 |
| Lorazepam 6 mg - Ganaxolone 2000 mg | 0 | 13.2 | 2.7 | 0.0000 | 8.7 | Inf | 7.8 | 18.6 |
| Ganaxolone 400 mg - Pcb | 11 | 4.5 | 2.3 | 0.0029 | -Inf | 8.3 | -0.1 | 9.0 |
| Ganaxolone 800 mg - Pcb | 11 | 5.7 | 2.3 | 0.0134 | -Inf | 9.6 | 1.0 | 10.4 |
| Ganaxolone 2000 mg - Pcb | 11 | 9.6 | 2.5 | 0.2889 | -Inf | 13.7 | 4.7 | 14.5 |

Note: Analyses were carried out in the Completers population. p-value was one-sided at alpha=0.05
LCL: lower confidence limit, UCL: upper confidence limit. M: -inf, I: inf. Pcb: Placebo.
* one-sided test; ** two-sided test.
Positice control vs. placebo (validation), $H_0$: $\mu_C - \mu_P <= Margin$
Positive controls vs. Test drug (Relative Abuse Potential), $H_0$: $\mu_C - \mu_T <= Margine$
Test drug vs. Placebo (Absolute Abuse Potential), $H_0$: $\mu_T - \mu_P >= Margin$

**Table 17. Inferential Analysis of Drug Liking VAS $E_{max(0-8h)}$ (Primary Endpoint) – Treatment Phase (Part B) (Completer Population)**

| Pairwise Comparison | Mean Difference (SE)[a]/ Median of Paired Difference (Q1, Q3)[b] | Confidence Interval | *P* Value |
|---|---|---|---|
| **Study Validity** | | | |
| Lorazepam 6 mg vs. placebo | 26.0 (12.0, 33.0)[b] | 20.0, 30.0 | **0.0069** |
| **Relative Abuse Potential** | | | |
| Lorazepam 6 mg vs. ganaxolone 400 mg | 18.1 (2.31)[a] | 14.3, 22.0 | < **0.0001** |
| Lorazepam 6 mg vs. ganaxolone 800 mg | 17.0 (2.66)[a] | 12.5, 21.4 | < **0.0001** |
| Lorazepam 6 mg vs. ganaxolone 2000 mg | 12.5 (4.5, 21.5)[b] | 8.0, 16.0 | < **0.0001** |
| **Absolute Abuse Potential** | | | |
| Ganaxolone 400 mg vs. placebo | 4.6 (2.51)[a] | 0.4, 8.8 | **0.0072** |
| Ganaxolone 800 mg vs. placebo | 11.0 (-2.0, 20.0)[b] | 5.0, 17.0 | 0.5000 |
| Ganaxolone 2000 mg vs. placebo | 13.0 (2.0, 26.0)[b] | 9.0, 19.0 | 0.6864 |

$E_{max(0-8h)}$ = maximum effect from 0 to 8 hours; Q1 = first quartile; Q3 = third quartile; SE = standard error; VAS = visual analog scale.

[a] Paired t-test was used to assess difference between 2 treatments; mean difference (SE), CI, and *P* value (alpha = 0.05) are presented.

[b] Sign test was used to assess difference between 2 treatments; median of paired difference, Q1 - Q3, CI, and *P* value (alpha = 0.05) are presented.

Notes: Drug Liking VAS was assessed by "At this moment, my liking for this drug is," where responses could have ranged from 0 (strong disliking) to 100 (strong liking) and 50 was the neutral point (neither like nor dislike).
Hypothesis 1: $H_0$: $\mu_C - \mu_P \leq 15$ vs. $H_a$: $\mu_C - \mu_P > 15$ where C = positive comparator; P = placebo.
Hypothesis 2: $H_0$: $\mu_C - \mu_T \leq 0$ vs. $H_a$: $\mu_C - \mu_T > 0$ where C = positive comparator; T = test drug.
Hypothesis 3: $H_0$: $\mu_T - \mu_P \geq 11$ vs. $H_a$: $\mu_T - \mu_P < 11$ where T = test drug; P = placebo.
Note that to aid with interpretation of the data, both sides of the confidence intervals are shown; however, the analyses were based on 1-sided testing.

**Table 16. Selected Descriptive Statistics of Drug Liking VAS $E_{max(0-8h)}$ – Treatment Phase (Part B) (Completer Population)**

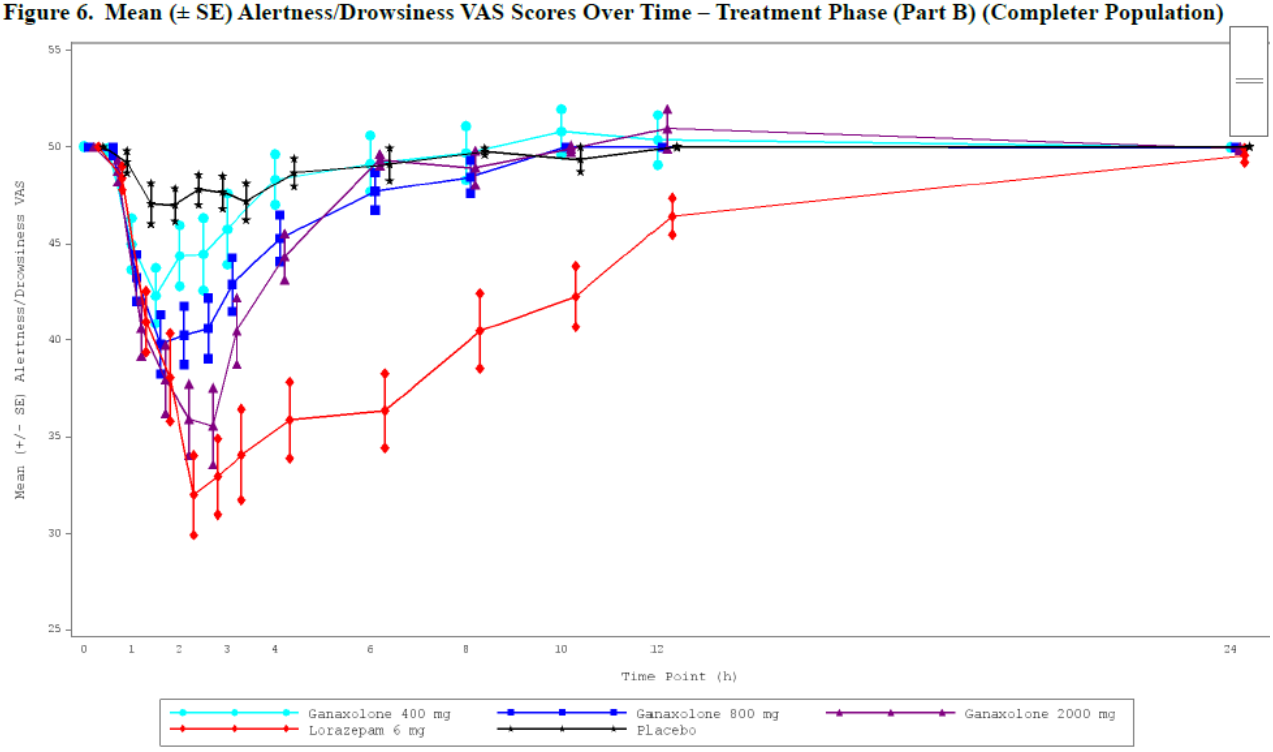
| | Ganaxolone 400 mg (N = 44) | Ganaxolone 800 mg (N = 44) | Ganaxolone 2000 mg (N = 44) | Lorazepam 6 mg (N = 44) | Placebo (N = 44) |
|---|---|---|---|---|---|
| **Drug Liking VAS $E_{max(0-8h)}$** | | | | | |
| Mean (SE) | 60.3 (1.89) | 61.5 (1.82) | 65.5 (2.13) | 78.5 (1.98) | 55.7 (1.57) |
| Median (Q1, Q3) | 56.5 (50.0, 68.0) | 57.0 (50.0, 73.0) | 63.5 (52.0, 76.0) | 79.0 (70.5, 86.0) | 50.0 (50.0, 58.5) |

**Table 18. Selected Descriptive Statistics of Overall Drug Liking VAS $E_{max}$ and Take Drug Again VAS $E_{max}$ – Treatment Phase (Part B) (Completer Population)**

| | Ganaxolone 400 mg (N = 44) | Ganaxolone 800 mg (N = 44) | Ganaxolone 2000 mg (N = 44) | Lorazepam 6 mg (N = 44) | Placebo (N = 44) |
|---|---|---|---|---|---|
| **Overall Drug Liking VAS $E_{max}$** | | | | | |
| Mean (SE) | 61.1 (2.49) | 62.6 (2.44) | 67.3 (3.23) | 77.5 (2.94) | 55.8 (2.43) |
| Median (Q1, Q3) | 52.5 (50.0, 73.5) | 56.0 (50.0, 74.5) | 65.5 (50.0, 84.5) | 79.5 (67.0, 94.5) | 50.0 (50.0, 59.5) |
| **Take Drug Again VAS $E_{max}$** | | | | | |
| Mean (SE) | 60.6 (3.06) | 63.2 (3.01) | 67.9 (3.70) | 80.4 (3.15) | 56.5 (2.63) |
| Median (Q1, Q3) | 51.5 (50.0, 74.5) | 56.0 (50.0, 77.0) | 66.0 (50.0, 87.0) | 84.0 (67.5, 100.0) | 50.0 (50.0, 60.0) |

$E_{max}$ = maximum effect; Q1 = first quartile; Q3 = third quartile; SE = standard error; VAS = visual analog scale.
Notes: Overall Drug Liking VAS was assessed by "Overall, my liking for this drug is," where responses could have ranged from 0 (strong disliking) to 100 (strong liking) and 50 was the neutral point (neither like nor dislike).
Take Drug Again VAS was assessed by "I would take this drug again," where responses could have ranged from 0 (definitely not) to 100 (definitely so) and 50 was the neutral point (neutral).
Source: Table 14.2.1.1.7.2 and Table 14.2.1.1.10.2.

**Figure 6. Mean (± SE) Alertness/Drowsiness VAS Scores Over Time – Treatment Phase (Part B) (Completer Population)**




SE = standard error; VAS = visual analog scale.
Notes: The y-axis has been truncated to assist with readability.
Alertness/Drowsiness VAS was assessed by "At this moment, my mental state is," where responses could have ranged from 0 (very drowsy) to 100 (very alert) and 50 was the neutral point (neither drowsy nor alert).

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